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OBSERVATIONS ON THE CYSTS OF *ENTAMOEBA TETRAGENA* *

S. T. DARLING, M.D.
ANCON, C. Z.

When we consider the medical history of Panama with reference to the origin of its population, the negroes from Africa and possibly the Pacific Islands, Chinese, introduced by the French Canal Company; Coolies, Sikhs and Bengalis from India, besides those representatives of the Caucasian race who have come from every portion of the tropical and subtropical world, Americans from the Philippines, various globe-trotters and "tropical tramps," we naturally expect to encounter here some of the diseases especially characteristic of other lands, and we are not surprised to find that echinococcus infections are confined strictly to Spanish laborers. Infection by *Taenia nana* and *T. saginata* occurs among Europeans and Americans. Bilharziosis comes almost exclusively from the French West India Islands, *Filaria demarquai* in negroes from St. Vincent, Old World hookworms, *A. duodenale,* among the West Indians, possibly introduced there by coolies. Trichinosis has been detected only among the Spanish (from Spain).

Some of these diseases are absolutely confined to the races or nationalities mentioned, because the local environment here is quite unsuited for their transmission to the native population. For example, there is no instance of any kind of tapeworm or fluke infection among the native population. It is otherwise, however, with hookworm disease. For the Old World worm is now found in many of the West Indians and in some Panamanians.

If a sailor infected with aestivo-autumnal malaria from the west coast of Africa should have a sufficient number of gametes in his peripheral blood on arriving here, and be bitten by *Anopheles albimanus,* 60 per cent. of the mosquitoes would become infected and might later transmit the disease to others; the secondary cases would clinically conform to the local type of malaria, and there would be no difference in morphology between the plasmodia and those in cases seen here.

*Manuscript submitted for publication in THE ARCHIVES Sept. 25, 1912.

If we compare too, the pathological features of those native diseases which are also found elsewhere in the tropical world, we find that they are practically identical. Oriental sore, black-water fever, yellow fever, leprosy and malaria present the same features wherever encountered.

To the practiced eye of the pathologist there is something specific about the appearances of the lesions caused by the pneumococcus, tubercle bacillus and meningococcus, when, for example, the meninges are involved, and a histological examination of tissue confirms the opinion based on the gross appearances. It is usually possible by a mere inspection of a temperature chart to distinguish from each other cases of relapsing fever caused by *Sp. recurrentis, Sp. duttoni and Sp. novyi.* If these premises are true, then if there be more than one variety of pathogenic entamebic infection it may be presumed that the cosmopolitan population of Panama would sooner or later disclose some evidence of the different types. For the disease requires no specific transmitting agent, but infection follows in the same way as typhoid fever or bacillary dysentery. We should expect to find at least the two alleged types described elsewhere, and we should expect to find some sufficiently well-marked differences in the lesions caused by the two species of entamebas. Such is not the case, however. In my autopsies at Ancon Hospital during the past seven years, the entamebic lesions have presented a characteristic, unique and unvarying pathology, and these lesions have the same character as those described from the Philippines and other tropical countries, if we are to judge from the descriptions and illustrations in the literature on the subject, and the opinions of medical men with a Philippine experience who have seen the cases here.

If we consider some of the protozoal diseases infecting man and animals, we may note that their sexual or perpetuating forms offer no difficulty of detection. Gametes of malaria may be found in almost every untreated case of malaria when carefully looked for. In coccidiosis of animals the oöcysts are always in evidence in the stools. Cysts of *Lambia intestinalis, Trichomonas vaginalis* and other intestinal parasitic flagellates are easily detected in the stools in cases of infection by their respective flagellated forms. Cysts of *Entamoeba coli* may be found in every case of infection by this entameba, and cysts of *Entameba tetragena* may also be found when specially looked for, in untreated cases not fatal, in imperfectly treated cases and in chronic cases, as well as in some cases before a relapse.

Is it not strange that the reproductive cycle of *E. histolytica* showing the formation of spores by budding has been so rarely seen? Schaudinn[1] described it from a case of dysentery contracted in China, and Craig[2] has

1. Schaudinn: Arb. a. d. k. Gsndhtsamte, 1903, xix, 547.
2. Craig: Am. Med., Phila., 1905, ix, 854, 897, 937.

confirmed Schaudinn's findings, while Hartmann,[3] who has examined some of Schaudinn's original preparations of *E. histolytica,* is of the opinion that most of them are *E. tetragena.* Practically all other observers of *E. histolytica* have had to content themselves with descriptions of the trophozoites of the large vegetative forms, or of the smaller forms, and on these they have based their determination of species.

If we make a careful study of the entamebas found in our cases of dysentery and liver abscess using a technic which brings out as well as possible the morphological features in the nucleus of the trophozoites and in the cysts, we can be of no other opinion than that there is but one pathogenic entameba and that one is *E. tetragena.*

We have too long been biased by the posthumous influence of Schaudinn. We have used too carelessly the Romanowsky stain with dry-fixed films for the identification of entamebas. We have been content to base our diagnosis on observations limited to the large trophozoite found in the stools in dysentery and in pathological tissue and to call the trophozoite "*E. histolytica.*" We have neglected to follow our cases during and after recovery, and we have failed to observe in neglected cases the forms representing the perpetuating phase of *E. tetragena,* namely, the small generation and the cysts, both of which have been overlooked or have been mistaken for *Entamoeba coli* and monad cysts.

We should give attention to the work of Hartmann, who, with his pupils, has established the fact that the common pathogenic entameba of all tropical and subtropical lands is *E. tetragena.*

While collecting and studying specimens of entamebas from clinical cases and autopsy material in Panama, I have had very little difficulty in observing nearly the complete developmental cycle of *E. tetragena,* but an insurmountable difficulty has been encountered in attempting to discover the first trace, in any of the entamebas seen here, of a developmental phase such as that described by Schaudinn and Craig, and I am forced to the conclusion that *E. histolytica* is not present in Panama; and influenced by the researches of Hartmann and Whitmore, by Walker's recent work in Manila, in connection with my own observations on tetragena cysts in the moist-chamber, and by animal experiments, I am inclined to doubt whether it has ever existed anywhere.

Great as Schaudinn undoubtedly was as a protozoologist gifted with a wonderfully penetrating mind in the observation of the life histories of protozoa, skilled in the difficulties of technic and possessing a scientific imagination of wonderful power in interpreting phenomena in his field, there is a steadily growing opinion that he made a number of errors. Novy has advanced reasons for believing that

3. Hartmann: Lehrbuch d. Protozoenkunde (Prowazek), Barth, 1911.

Schaudinn was mistaken with regard to the life history of *Trypanosoma noctua,* and Hartmann as mentioned above believes that he was misled by degeneration forms in describing *E. histolytica.*

Schaudinn studied the peculiar forms from which he described *E. histolytica* in but one single case of entamebic dysentery, and his interpretations have been accepted and applied to many cases elsewhere by several observers. If *E. histolytica* be the common entameba of tropical lands as we have hitherto supposed, it is extraordinary that so little testimony has been adduced in evidence that this entameba has existed in any other person than Schaudinn's Chinese case. It is true that Craig has confirmed Schaudinn's work in connection with the development of entamebas by spores. But Craig's illustrations indicate that some at least of the forms drawn by him as *E. histolytica* were *E. tetragena* and that his technic was not calculated to bring out such distinctions as are necessary for the purpose. In studying the spore formation of *E. histolytica,* Craig seems to have relied on dried[4] films stained by a modification of the Romanowsky stain. If one collects from the literature the illustrations of *"E. histolytica"* and of *E. tetragena* and compares them it will be seen at once that the writers have been calling *E. histolytica* the large trophozoites seen in dysenteric stools; these frequently display no karyosome but they can be demonstrated as *E. tetragena* by animal inoculation or by the history of the case. On the other hand the illustrations of *E. tetragena* show that the writers have been dealing with the reduced forms or small generation which are the lineal descendants of the large trophozoites. Elmassian indeed, a trained protozoologist, working with the reduced form of *E. tetragena,* described it as *"E. minuta,"* a distinct species.

The importance of Craig's work is in insisting on the truth that there are two parasitic entamebas for man, *E. coli* and a pathogenic form, and we owe to him a considerable debt of gratitude for this work, for he was for years the chief if not the sole influence in America opposed to the sincerely advocated but pernicious views of the culturalists, or those who believed (in fact some still believe) that the pathogenic entameba may be cultivated on protozoal agar.

The subject is of more than academic importance, for now that Hartmann has established the wide-spread distribution of *E. tetragena* and all our cases of dysentery here are caused by the same entameba, we should begin at once the investigation of some of the important questions vital to this disease, such as the viability of *E. tetragena* cysts in the outside world; the conditions in the host which lead to the pro-

4. In a strain of *E. tetragena* from kittens I found artefacts in certain films that had been dry-fixed and stained by Romanowsky. These might easily have been described as the budding forms and spore formation of *E. histolytica.*

duction of cysts; the influence of medication on cyst production; the susceptibility of domestic animals to infection and their agency as carriers; and the number and kind of cysts necessary to infect. It is this aspect of the question that is of greatest importance.

It would seem that infection in man occurs through the mouth by the ingestion of cysts. In two recent cases a cook and a child in the family who harbored cysts appeared to be the carriers. The individual with acute symptoms of dysentery is not usually infectious, for he is merely harboring the large vegetative form, which, to judge from the results of animal experiments, is digested and cannot serve to infect. It is the unsuspected individual who has recovered from an attack and who may have formed stools or possibly diarrhea, whose stools contain cysts that is the carrier of infection. The importance, therefore, of examining stools of recovered patients, and in fact all clinical cases, as well as of persons in contact with clinical cases of dysentery, for the detection of carriers, is very great. I have detected cysts in several individuals in whom they were unsuspected. The commonest location for entamebic lesions in our cases here has been the cecum. Cases of this type may give no evidence of infection other than colicky pains in that region, but they are undoubtedly fertile carriers of cysts. The stools of cyst-carriers are usually solid and contain no dysenteric elements—one of the reasons why tetragena cysts have been so long overlooked or misinterpreted.

The cysts are round, refractive bodies about 15 microns in diameter. They have no doubt been mistaken for monad cysts, but may be differentiated from them by the fact that the latter vary a good deal in size, are either smaller or larger, and have crescentic margins. The cysts may be seen in fresh preparations to have one, two, or four nuclei; some have refractile blocks of chromidia. When the cysts are quite homogeneous in the fresh stool, they will after exposure to the moist chamber or in vaselined films become differentiated in a day or two so that one, two, or four nuclei may be seen. In some preparations after several days in the moist chamber it is possible to note that the cysts contents are ameboid, and rarely, if one is fortunate, the emergence of amebulae may be noted. When it is desired to stain them, films should be made, wet-fixed and stained with hematoxylin.

The mode of treatment appears to have a very important relation to cyst production. I have observed cysts in several chronic and untreated cases and in a patient treated by means of rectal injections which probably did not reach the lesions higher up; but I have detected cysts in only one case in twenty-eight that had been treated by means of very large doses of bismuth subnitrate. In these cases the stools contained from 9 to 10 per cent. by weight of bismuth subnitrate. It

would appear that when most cases of entamebic dysentery are treated energetically by this medicament, the vegetative or large pathogenic generation is at once removed, leaving none to propagate the small generation from which the cysts arise.

Cases treated energetically by oral medicaments may fail to disclose cysts, for the vegetative entamebas do not have time to develop a resistant small generation with cysts. This is analogous to the destruction of all malarial merozoites by means of large doses of quinin at the beginning of an attack and thus killing all the potential gametes.

The investigations of Hartmann,[5] Viereck,[6] Werner[7] and Whitmore[8] have shown the wide-spread distribution of *E. tetragena* as a cause of entamebic dysentery. The paucity of evidence which we possess on the subject of the perpetuating forms of *E. histolytica;* and the likelihood of *E. tetragena* being the chief, if not the sole, cause of entamebic dysentery in man, leads me to report these observations, for I am unaware of any published records of observations on the fate of *E. tetragena* in the outside world. Material from three cases has been studied.

CASE REPORTS

CASE 1.—Hospital No. 105,730. This case was the first one positively identified here as an infection by *E. tetragena*. The patient was admitted Sept. 5, 1911. It was his first time in the hospital. His complaints were referable to an infection by malarial plasmodia which were found in his blood. He stated that his bowels were regular. He remained in the hospital fourteen days, received 3 grains of calomel and three doses of magnesium sulphate. The total number of stools for the period was 51, an average of 3.6 daily. On one occasion it was noted that pus was found in the stool; this was on September 14. On September 8 many small entamebas (Fig. 10) were detected in the stool and these I identified as *E. tetragena*. The patient was discharged September 19, and returned to work. In this case there is no history of dysentery. Evidently the lesion in the colon was high up; most probably in the cecum.

The stool of November 13 contained trophozoites, schizonts and cysts, and in stained specimens four nucleated cysts were detected.

Through the kindness of Drs. Connor and Weinberg I obtained specimens of the man's stool after he had returned to work. The stools were solid but contained many small tetragena cysts. All of those observed were homogeneous, for nuclei and chromidial blocks could not be detected in the fresh specimen. Cultures on protozoal agar and tap water broth were entirely negative for trophozoites, and cysts disappeared completely from the stools and cultures within seven days.

On November 13 vaselined coverslip preparations were made with the fresh stool. The cyst contents appeared perfectly homogeneous, nuclei and chromidial blocks were not seen. November 14 the interior of the cysts had become coarsely

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5. Hartmann: Handbuch d. Path. Protozoen (Prowazek), Barth, Leipzig, 1911, Installment 1.

6. Viereck: Studien über die in den Tropen ewarhene Dysenterie, Beihefts z. Arch. f. Schiffs- u. Tropenhygien, 1907, No. 11.

7. Werner: Studien über pathogene Amöben. Beihefte z. Arch. f. Tropen- und Schiffshygiene, 1908, xii, part II.

8. Whitmore: Arch. f. Proteitenkunde, 1911, xxiii 1; Centralbl. f. Bakteriol., Orig., 1911, lviii, 234.

granular. November 15 many of the cysts were seen to have four nuclei imbedded in finely granular protoplasm. November 18 there was a space between the cyst capsule and the granular central mass. The latter had become mulberry-like in form and was seen to slowly move on itself in an ameboid fashion. The nuclei within the mass were from time to time plainly discernible, disappearing as they rose or fell from the optical plane during the ameboid motion (Fig. 14). Some of the cysts were filled out completely by the granular mass. Some had two nuclei, others had four, while some had no nuclear figures at all. The protoplasm was always granular. A motile bacillus was seen in the subcapsular space in several specimens. The capsule of some became invisible as though of the same refractive index as the surrounding medium. A number of the cysts had disappeared at this time, for the number was very definitely reduced.

CASE 2.—Sr. A. April 9, 1912. The patient was an adult male living in the city of Panama. He was suffering from an attack of entamebic dysentery and his stools contained much bloody mucus and many entamebas. With gentian violet by the *intra vitam* method the submembranous granules of the nucleus of the entamebas stained distinctly and some individuals had a faintly staining centriole and others appeared to have a faintly staining karyosome. Rectal injections of the infected stool eight hours old into very small kittens were negative. Hematoxylin-stained preparations showed the trophozoite to be of the large vegetative type in which the karyosome was only seen in certain individuals and did not stain at all deeply. Dry fixed preparations stained by Hasting's and Giemsa's stains showed the nucleus as containing a fine red oxychromatin reticulum not usually arranged in the form of a ring.

The patient was placed on treatment by his physician in Panama. This consisted of astringent rectal injections. He has reported to me from time to time, on each occasion bringing a specimen of his stool. On May 20 he returned from the interior appearing to be in much better physical shape and free from dysentery. A specimen of stool just passed was free from dysenteric elements but contained many one, two and four-nucleated tetragena cysts all containing blocks of chromidia (Figs. 7, 11 and 12).

On June 13 the patient returned with a specimen of hard formed stool. He stated that he had had no return of dysentery, but was continuing the rectal injections. The stool contained many tetragena cysts, and portions were placed in a moist chamber and in sterile tap water, to note developmental changes. June 27 no cysts could be detected in the patient's stool, which was a solid one. July 17 a good many tetragena cysts were found in specimens of a formed stool passed this morning: all contained nuclei and chromidia.

Summary of Findings: April 9 the stool contained pus, blood, mucus, and many large trophozoites; only a few of the latter revealed a karyosome when stained by gentian-violet and iron-hematoxylin. In other words, most of the trophozoites would be described as "*E. histolytica*." Rectal injections of the stool eight hours old into two very small kittens failed to infect.

May 20, the stool was formed and contained no vegetative trophozoites, but many one-, two-, and four-nucleated cysts of *E. tetragena*. In moist-chamber preparations, all the cysts disappeared within five days. Feeding experiments on very small kittens with cysts from this stool on the day of passing were negative.

June 13 the stool was formed and contained many tetragena cysts but no trophozoites. In moist-chamber preparations the cysts rapidly diminished in numbers so that very few were seen at the end of twenty-four hours. No cysts could be demonstrated at the end of six days in hematoxylin stained preparations and none could be demonstrated in coverslip preparations of the six- and ten-day-old-stool. Preparations of the stool which had been put up with sterile tap water for nineteen hours contained some four-nucleated cysts (Fig. 13).

About 10 grams of feces that had been in the moist chamber for three days, were taken up with water and milk and passed into the stomach of two half-grown cats, but no infection resulted during a period of eight weeks.

EXPLANATION OF FIGURES IN PLATE

1. The large trophozoite (Phosphotungstic acid hematoxylin) endoplasm and erythrocytes are shown, the centriole and karyosome and peripheral chromatin are conspicuous.

2. Trophozoite with primary division of nucleus into four nuclei. This form is rarely seen and is believed to be a schizont; it may become the form seen in Fig. 3.

3. Four nucleated trophozoite (schizont?).

4. Trophozoite gamete (?) seen in Case 3, May 14, apparently a larger size of 5 and 6.

5. Trophozoite gamete (?) of small size seen in Case 3, May 14, probably a larger form of 6.

6. Small trophozoite gamete (?) arising from a cyst.

7. Trophozoite of small generation becoming encysted; central sac of fluid (?) and blocks of chromidia are shown.

Two trophozoites (gametes ?) from Case 3, May 14; a number of couples were seen together in this way; the nuclei were always of different types. The ectoplasm was apparently sticky for the organisms could not separate, but moved around and around.

9. Trophozoite of small generation becoming encysted; the nucleus is vesicular and the chromidia is seen condensing around the periphery of the fluid sac.

10. Trophozoite of the small generation containing chromidia.

11. Binucleated cyst containing chromidia. One of the nuclei shows division of its centriole.

12. Quadrinucleated cyst.

13. Quadrinucleated cyst unstained, from moist chamber preparation, second day; the cyst contents are homogeneous save for 4 nuclei represented by peripheral refractile granules of chromatin.

14. Mulberry mass in a cyst from moist chamber, fifth day, contains four amebulas with granular cytoplasm, nuclei and amœboid outline unstained. One nucleus is not displayed as it was not in the optical plane.

15. Mononucleated cyst containing two blocks of chromidia, one of the type that stains unusually deeply.

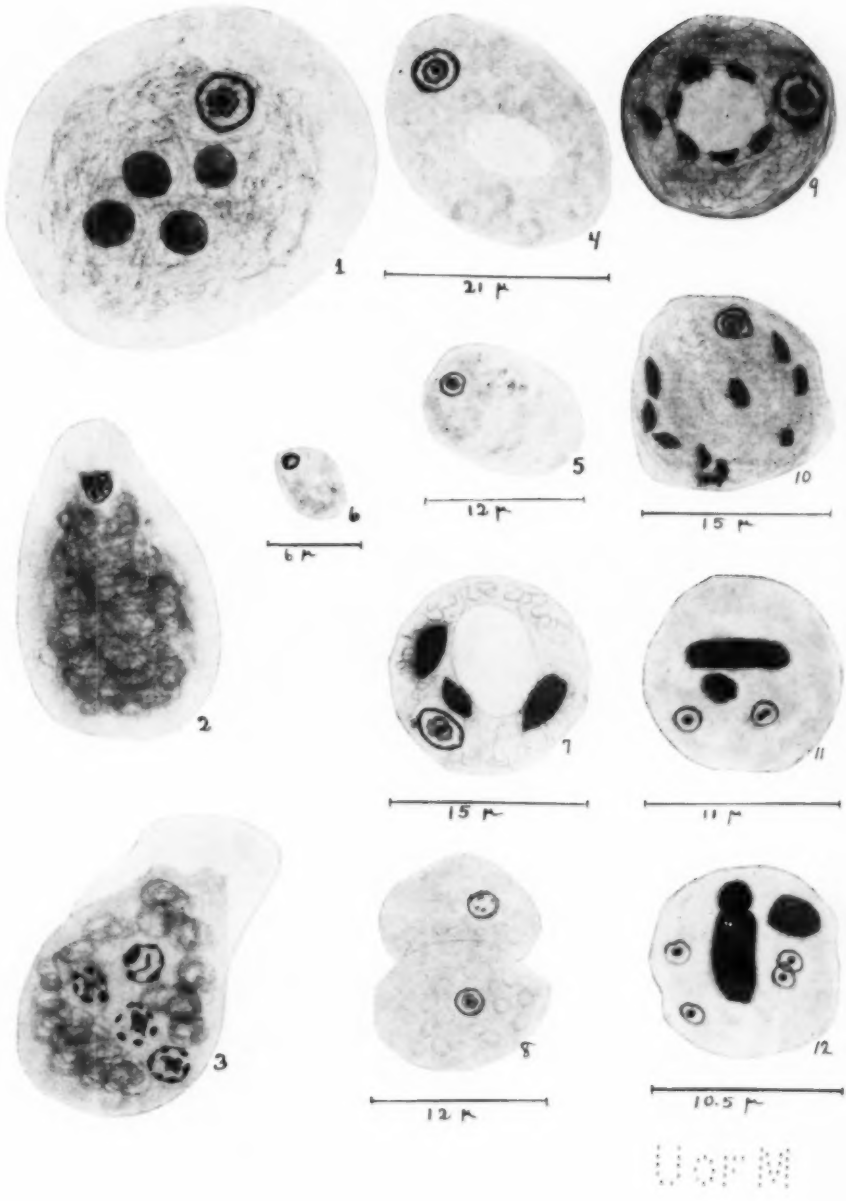
16, 17, 18, 19. Mononucleated cysts from moist-chamber preparations forty-eight hours old; the last three showing a fluid sac.

20-23. Binucleated cysts from moist-chamber preparations, forty-eight hours old.

24. Quadrinucleated cyst.

25. Cyst from moist-chamber after four days. One of the amebulas (gametes ?) has become separated from the rest though it is still enclosed by the capsule of the cyst. Two of the nuclei stain well; one apparently has degenerated.

Note.—No. 3 was stained with iron hematin after fixation with Schaudinn's fluid; No. 1 with phosphotungstic acid hematoxylin after Zenker fixation. This shows the effect of technic in transfixing and displaying variously the nucleus, particularly the karyosome ring.



ILLUSTRATING ARTICLE BY S. T. DARLING, M.D.

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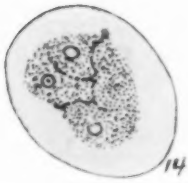
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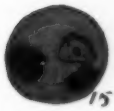
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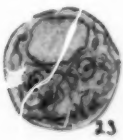
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Illustrating Article by S. T. Darling, M.D.

Microfilm

Smear preparations of the moist chamber specimens contained only one cyst in three films, a considerable reduction of numbers within seventy-four hours.

A quantity of the stool that had been put up for three days with ten volumes of sterile tap water was added to diluted milk and passed into the stomach of two kittens, but no infection resulted in a period of over eight weeks.

Six coverslip preparations from the stool that had been in contact with tap water for three days were quite negative for cysts; apparently a complete disappearance of cysts when in contact with water for this period of time.

June 27, no cysts nor trophozoites were detected in the stool, which was well formed.

July 17 the formed stool contained a good many cysts (three or four to the high, dry field). After twenty-four hours in the moist chamber, there was an appreciably smaller number, and after forty-eight hours, very few cysts could be detected.

In this case, the gradual disappearance of cysts in cultures is seen and the lack of infectiousness of the stool for kittens after three days, probably due to an insufficiency of cysts. This case shows too the persistence of cysts in a patient treated by means of rectal injections which do not reach the upper portion of the large bowel, namely, the cecum, where the commonest location of the entamebic process is. The absence of cysts from the stool on one occasion as well as their appearance in solid stools is also noted.

Case 3.—Hospital 111,761. I had an opportunity of examining material from this case through the kindness of Drs. James and Carter. The patient had been treated for entamebic dysentery, and on Jan. 11, 1912, a specimen of his stool contained trophozoites and cysts which I identified as *E. tetragena* (Fig. 9). On April 2, the patient had returned to the ward for treatment and his stool on this date contained scybala with bloody mucus containing many large trophozoites such as are usually found in entamebic dysentery (Fig. 1). The trophozoites were about 30 microns in diameter, were finely granular and possessed a rather unusual mode of locomotion. They moved from place to place with a rolling, flowing motion, rather more continuous than intermittent.[9] Some had phagocyted erythrocytes. When stained with hematoxylin, they showed a well defined karyosome, but no cysts nor trophozoites with chromidia were detected. The dysentery disappeared after a few days and on April 11 and 12 a few cysts were seen. A solid stool on April 12 contained a few trophozoites which were very refractile and were stained *intra vitam* by gentian-violet. The stain was taken up slowly but intensely, and revealed a typical tetragena nucleus with a well defined karyosome.

On May 14 the patient's stool contained enormous numbers of cysts and small-sized trophozoites. These were placed in moist chambers and examined from day to day after fixation in Schaudinn's fluid and staining with hematoxylin.

Fresh Stool of May 14.—One is struck at once with the appearance and large numbers of the small trophozoites. Sixty-five per cent. are trophozoites and 35 per cent. are cysts. These trophozoites (Fig. 4) are about 21 microns in length by 12 microns in breadth. They have conspicuous nuclei, many of them showing rather deeply stained karyosomes and the so-called cyclical changes in the centriole. The cytoplasm is vacuolated, the vacuoles being three microns and under in diameter. Many have engulfed bacteria but none had phagocyted erythrocytes. None of these trophozoites contained chromidia, but they are associated with spherical or slightly ovoid cysts 12 to 15 microns in diameter, which contain one

9. Trophozoites of *E. tetragena* have two types of motion; an impulsive intermittent one seen in the large, globular, refractile forms, and the flowing continuous motion seen in the elongated non-refractile forms.

or more coarse blocks of chromidia (Fig. 7). There is usually a large fluid- (?) containing sack or vacuole and a conspicuous nucleus. Sometimes there are two or four nuclei. It would appear that these cysts have developed from the trophozoites with which they are associated. Besides these forms there are some smaller trophozoites ranging in size from about 4 microns up to full size (Figs. 5 and 6). Some have nuclei exactly like those of the four-nucleated cysts and they are undoubtedly derived from them. A few four-nucleated forms, however, are seen which do not appear to be encysted. They are usually elongated and not spherical. These are undoubtedly four-nucleated schizonts. Confirmatory of the opinion that this is their nature, I may say that I have seen a few naked four-nucleated forms (Fig. 3) in the pus from an entamebic liver abscess (autopsy 2,760), and these four-nucleated forms were associated with a few small amebulas as well as large trophozoites. In the stool of Case 3 on January 11, I observed a trophozoite, the nucleus of which had divided into four small daughter nuclei (Fig. 2); these were in apposition and occupied the place and area of that of an ordinary sized nucleus of a trophozoite; it was undoubtedly becoming a four-nucleated schizont. Fifty per cent. of the cysts are uninucleated; 23.5 per cent. binucleated; and 26.5 per cent. quadrinucleated.

Moist-Chamber Preparation After Twenty Hours.—At this time it is evident that many forms have disappeared. Apparently there has been a reduction of 50 to 75 per cent. in the total number, due chiefly if not entirely to the complete disappearance of the trophozoites. The forms now seen are encysted (Figs. 15 to 24) and resemble those cysts seen in the fresh stool, although most of the chromidia has now disappeared. A few cysts present appearances indicating most positively an ameboid movement within the cyst wall, and the emergence of amebulas. It is these small amebulas which are the precursors of the "agamous" trophozoites, concerned in entamebic dysentery. For infection follows the feeding of cysts while it invariably fails when only the trophozoites are fed. There is still a number of small amebulas (Fig. 6) to be seen but no gradation of sizes and no full sized trophozoites (Fig. 4). It is evident that the amebulas perish in the fecal mass in moist-chamber preparations. This is in contrast with the appearance noticed in the fresh stool for in the favoring environment of the intestinal tract the young amebulas had increased in size.

Moist-Chamber Preparation After Forty-Eight Hours.—There is a still further reduction in the number of cysts, the cytoplasm of which appears to be more homogeneous and usually free from the achromatic sac of fluid (?) noted previously. The cysts are round or ovoid. Rarely one contains chromidia. A few small free amebulas are seen but no full-sized trophozoites.

Moist-Chamber Preparation After Three days.—A still further reduction in the number of cysts. Four nucleated forms appear to predominate. Otherwise, the preparations resemble those of the day before.

Moist-Chamber Preparation After Four Days.—The number of cysts appears to be reduced over those in yesterday's preparation. It is impossible to estimate this accurately, however, from smears. Several cysts to-day contain traces of eroded chromidia as though it had been etched off the surface for nutritive purposes. A number of cysts are somewhat irregular in contour and represent the ameboid changes noted on previous days, and in cover-slip preparations from Case 1. Some free amebulas are seen (Fig. 25).

Moist-Chamber Preparation After Six Days.—Very few cysts are seen, and considerable time is required to find a sufficient number on which to make observations. The irregular contour of the cyst contents is even more exaggerated than in yesterday's preparation.

These changes noted in the cysts are analogous to those seen in *E. coli*, and differ entirely, of course, from those to be seen in free-living forms.

The cysts require a moist medium for their development. Drying interferes with nuclear division and emergence of amebulas from the cysts. This is seen from the following experiment: About 5 grams of feces from Case 3 on May 14,

containing many cysts and trophozoites of the small generation, were spread over the surface of a porous plate which had been sterilized within a petri dish. The porous plate absorbed moisture from the feces and the resulting film remained as dry as the surrounding atmosphere. After a period of seven weeks the film was moistened with sterile tap water and smears were wet-fixed and stained with hematoxylin. The resulting picture was just like that of the fresh stool, excepting for the change due to desiccation. The trophozoites and cysts took the stain very well, particularly the nuclei and chromidia, but they presented a flattened out and warped appearance.

The larger portion of the moistened film was fed to two half-grown cats, but no infection resulted, although this would certainly have provoked entamebic enteritis if the same amount of fresh material had been used.

This is interesting in comparison with Schaudinn's experiment in which he claimed to have induced infection in a cat with dried material containing spores of *E. histolytica* six weeks old.

The developmental changes in the cysts of *E. tetragena* can best be studied in just such a case as the one described, in which there is an enormous number of encysting forms, and these forms appear in some cases in perfect showers.

It would seem that the large "agamous" trophozoites luxuriate during the acute stage and in active lesions associated with tissue necrosis where nutrition is plentiful. As a result of immunity on the part of the host, or from other causes not as yet known, a reduction in size in the trophozoite occurs. Pearl[10] and Calkins[11] have shown that the "conjugating generation of *Paramecium* consists of individuals of measurably smaller size than those of the usual pond water. There is also a difference in the physical and chemical make-up of the cells by which the protoplasm becomes much more sticky, so that two individuals upon meeting frequently fuse at any point." This is referred to because of the fact that the generation immediately preceeding the cysts is very much reduced in size and in the fresh stool of Case 3 on May 14, a number of trophozoites were seen as though partly fused together, and possibly represented conjugation. In all cases of infection by *E. tetragena* either in the bowel or liver, a few smaller forms 15 to 24 microns in diameter may be seen, and forms containing chromidia may also be detected when specially looked for. I have seen in a fatal case large trophozoites 30 to 40 microns in diameter, deep in the submucosa, while in the superficial sloughs of the ulcer only small refractile forms were seen. In the fresh preparations nuclei could not be demonstrated in the smaller forms, and when they were treated *intra vitam* with gentian-violet, they took up the stain with extreme slowness compared with the larger more deeply lying trophozoites. These smaller forms are about 15 microns in diameter and contain

10. Pearl: Biometrical Study of Conjugation in *Paramecium*. Biometrica, 1907, v, No. 3.

11. Calkins: Protozoology, 1909, Lea and Febiger, New York and Philadelphia.

no erythrocytes but several blocks of chromidia. This small chromidia-containing generation occupies a stage between the large trophozoites and the cysts.

The appearances in the cysts with regard to fertilization have been interpreted variously. Hartmann[12] and Doflein[13] have figured and described changes which they interpret as autogamy, while Walker[14] sees only a straight forward nuclear division in the cysts. Elmassian,[15] who studied most minutely in a mixed infection of *E. coli* and *E. tetragena*, the small generation and cysts of *E. tetragena* under the name of *E. minuta*, has described appearances which he has interpreted as autogamy. In the very rich collection of cysts furnished by Case 3 on May 14, I have failed to find positive evidences of autogamy such as have been figured by Hartmann and Elmassian, in spite of the fact that I have used phosphotungstic acid hematoxylin, which is probably the most accurate of hematoxylin stains for entamebas fixed with diluted Zenker's and Flemming's solutions.

In the stool of Case 3 on May 14, there is one feature rather difficult to explain. The trophozoites (Fig. 4) are 15 to 16 microns in diameter, always devoid of erythrocytes and usually devoid of chromidia, differing thus from pathogenic trophozoites (Fig. 1) and the common small-chromidia-containing generation (Fig. 10) respectively. The trophozoites contain bacteria, and have evidently been living a vegetative existence in the lumen of the bowel, but although they contain no chromidia they are associated with cysts which nearly always contain several blocks of chromidia (Figs. 11 and 12), and they are associated also with small and half grown trophozoites (Figs. 5 and 6) exactly like them in staining characters. Is it possible that these trophozoites (Fig 4) have developed in the bowel from cysts and are living a parasitic and non-pathogenic existence in the intestinal lumen, but which would take on an appearance like the pathogenic trophozoite after they had gained entrance to the bowel wall? The very small forms have arisen from cysts or from schizonts, most certainly from the former, for the latter were rarely seen, and these very small forms in turn may develop into the trophozoites just described. If this is true, the precursors of the cysts, which we should expect to contain chromidia, are not present in this specimen. On the other hand, if the cysts develop from the non-chromidia-containing trophozoites, when does the chromidia appear on the scene? for the non-chromidia-containing trophozoites disappear

12. Hartmann (Handbuch d. Path. Protozoen (Prowazek), 1911, Barth, Leipzig) more recently would seem to be of the opinion that *E. tetragena* is analogous to *E. blattarum* and does not exhibit autogamy.

13. Doflein, F.: Lehrb. d. Protozoenkunde. Ed. 3, Fischer, Jena, 1911.

14. Walker: Philippine Jour. Sc., 1911, vi, 259.

15. Elmassian: Centralbl. f. Bacteriol. Orig., 1909, lii.

completely in twenty hours, at which period there were many chromidia-containing cysts. Unfortunately it is impossible to determine from these preparations whether the trophozoites all perish or whether they develop into cysts. I am inclined to believe that they perish in the moist-chamber for the number of cysts seen on May 15 was about the number seen on May 14, minus the trophozoites. It will be important in the future to note from hour to hour the changes in the small generation.

The chromidia of the cysts appeared to be used up in the course of nuclear division, for its margins usually became eroded (Fig. 24), yet in some four-nucleated cysts uniformly contoured blocks of chromidia were seen (Fig. 12).

Counts of the different types of cysts and trophozoites were made from day to day and from different films, and are here tabulated.

COUNTS OF THE DIFFERENT TYPES OF CYSTS AND TROPHOZOITES IN A RECENT STOOL MAY 14 (CASE 3)

Trophozoites, 15 microns in diameter containing bacilli but no r. b. c. with prominent karyosome ring; no chromidia 48.3 per cent. Cysts 34.9 per cent.	Half-grown trophozoites 9.6 per cent.	Very small, recently emerged trophozoites 5.6 per cent.	Four-nucleated schizonts 1.6 per cent.

Recent Stool of May 14.....	Percentage of Different Forms in Moist-Chamber Preparations After					
	Recent	20 Hrs.	2 Days	3 Days	4 Days	6 Days
One-nucleated cysts	50	47	50	31	34	33
Two-nucleated cysts	24	20	18	27	25	33
Four-nucleated cysts	26	33	32	42	41	33
Number of individuals counted	67	*101	*109	*102	*24	*15

*Very small amebulas were present but could not be counted with any accuracy.

The stool was a pure culture of *E. tetragena*, as were stools in Cases 1 and 2, and the moist-chamber preparations were kept in sterile petri dishes and handled carefully so as to avoid aerial contamination by free-living forms. Fortunately, free-living forms did not develop in any of the preparations, though it is not an uncommon experience for them to appear in cultures of feces. Smears were made and wet-fixed with Schaudinn's bichlorid alcohol and stained with hematoxylin. Good results were obtained with iron-alum-hematoxylin and phospotungstic acid-hematoxylin with a final differentiation by means of potassium permanganate.

Two half-grown cats were fed with material from the stool of May 14 that had been in a moist chamber forty-eight hours. Both animals had prolapse of the rectum at nearly the same hour, twelve days later. The prolapse followed intussusception starting from an inflammatory patch in the lower ileum from which many large trophozoites were obtained. *These trophozoites, although arising from tetragena cysts, presented the nuclear characteristics of E. histolytica, E. tetragena and E. nipponensis.* From this experiment, it can be seen that identification of species cannot be based on appearances noted in the "agamous" trophozoites, and further, it is seen that the alleged differences between *E. tetragena* and *E. histolytica* and *E. nipponensis* are due to unusual physiological or pathological distributions of basichromatin within the nucleus of *E. tetragena.*

CONCLUSIONS

These cases illustrate the cyst production of *E. tetragena,* its intermittency, the absence of cysts during acute symptoms and their presence in formed stools long after the subsidence of acute symptoms.

The gradual disappearance of cysts in moist chamber preparations with a concomitant loss of infectiousness of the stool, and the loss of infectiousness by drying for seven weeks are shown. The development of amebulas within the cysts and their emergence and fate in the fecal mass is described.

It would appear that infection in man is the result of the contamination of food with a small amount of fecal matter containing a great many cysts, during the first day or two after passing.

In one experiment, kittens were fed with a pure culture of tetragena cysts forty-eight hours old. This caused lesions in the small bowel in which large trophozoites were found with the nuclear characters of *E. tetragena, E. histolytica* and *E. nipponensis.* This not only favors the opinion held of the identity of *E. histolytica* and *E. nipponensis* with *E. tetragena,* but it shows that specific identification of histolytica and nipponensis cannot be made from the large vegetative trophozoites alone, but the essential features of the life cycle must be seen.

The very great importance of examining the stools of all convalescent and recovered cases of entamebic dysentery for cysts, and thus detecting "carriers" is made apparent, for it is the cyst that is the infecting agent and not the large trophozoite.

SYPHILITIC AORTITIS: ITS DIAGNOSIS AND TREATMENT *

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For some years I have been much interested in the condition which is now generally known as syphilitic aortitis or mesaortitis. At first my observations were particularly directed to the pathological lesion itself; later the exact etiology of these changes became the subject for study, while at present it is the diagnosis and treatment of the disease to which most time is devoted. Up to the present I have had an opportunity at the Pennsylvania[1] and University hospitals in Philadelphia, and at the Presbyterian Hospital in New York of studying sixty-three cases in which syphilitic aortitis was proved to exist at autopsy, or in which the diagnosis seemed reasonably sure from the combination of certain symptoms and signs, with a positive Wassermann reaction during life. Of the entire number, twenty have been treated with salvarsan. But except for the fact that the diagnosis and treatment of this disease are of such importance, and that the observations have perhaps suggested certain lines for further study, it would scarcely be justifiable to offer such a familiar subject for serious consideration.

Since the time of Morgagni, syphilis has been recognized as a factor in the etiology of aneurysm, as well as of other less well defined cardiovascular diseases, but it was not until the publication of the anatomical studies of Döhle,[2] in 1888, followed by the work of Heller and his pupils on syphilitic aortitis that the direct relationship between the two was made apparent. Döhle's excellent description and illustrations of the pathology of syphilitic aortitis really leaves little to be added on that score, while the accounts of the French, and particularly Huchard,[3] Dieulafoy,[4] Gallavardin[5] and Fournier[6] of the symptomatology and diagnosis of *"Aortite sub-aigué,"* a subject to which they have devoted much attention, and to which Germans and Anglo-Saxons until recently have paid comparatively little heed in spite of the original account by Cor-

*Submitted for publication in the ARCHIVES Oct. 21, 1912.

1. For an opportunity of studying the cases at the Pennsylvania Hospital I am indebted to Drs. Morris J. Lewis, J. C. Wilson, James Tyson, J. Norman Henry, Alfred Stengel, and the late Dr. Arthur V. Meigs.
2. Döhle: Deutsch. Arch. f. klin. Med., 1895, lv, 190.
3. Huchard: Traité clinique des maladies du coeur et de l'aorte, Paris, 1899.
4. Dieulafoy: Clinique medical de l'Hôtel Dieu, Paris, 1896-7, p. 71.
5. Gallavardin: Precis de maladies du coeur et d l'aorte, Paris, 1908.
6. Fournier: Traité de la syphilis, 1899.

rigan,[7] and the articles of Allbutt,[8] cover this aspect of the disease in a fairly thorough manner. The more recent lectures of Mitchell Bruce,[9] Schwarz,[10] Breitmann[11] and Goldscheider[12] also contain good clinical descriptions.

The important conclusion of Döhle that syphilis produced a characteristic type of aortitis brought forth some adverse criticism, but no very wide-spread interest, and it was not until the subject was presented before the Deutsche Pathologische Gesellschaft in 1903 by Chiari,[13] Benda[14] and Marchand[15] that arteritis became a common subject for study. During the following years many papers appeared giving anatomical descriptions and statistical records, but as this literature is thoroughly reviewed in Fahr's[16] paper, and in Herxheimer's[17] excellent article, it is unnecessary to do more than refer to these publications. Indeed, the morbid anatomy of the process has been made so familiar through numerous original contributions, as well as by descriptions and pictures in recent text-books such as those of Adami and Aschoff, that it seems scarcely necessary to give more than the briefest outline of the anatomical changes as I have observed them.

ANATOMICAL CHANGES

The gross appearances of syphilitic aortitis are in themselves fairly characteristic. The root of the aorta and the arch are most commonly affected, but the process may be found anywhere throughout the length of the vessel. In several instances I have seen an extensive, though circumscribed process in the abdominal aorta. The lesion as a rule is quite sharply confined to a certain area. The smallest areas and probably the earliest which we can recognize consist of well outlined, pale grey, rather translucent, elevated, succulent looking patches 0.5 to 2 or 3 cm. in diameter. On section the elevated portion of the vessel is translucent and grey; beneath this and corresponding to the media one sees opaque, yellow streaks and patches running the length of the section, and sometimes 1 to 2 mm. in thickness. These occasionally sink beneath the level of the knife cut. The larger and more advanced areas form isolated or conglomerate patches 4 to 10 cm. in diameter, or completely surround the circumference of the vessels. The distal margin is usually very sharply defined, and beyond this line of demarcation, which may be found somewhere along the arch, the smooth, delicate aorta stretches in wonderfully sharp contrast to the diseased portion. The surface of the larger areas is extremely irregular. The elevated patches mentioned above alternate, or are irregularly intermingled with yellowish, scarred, pitted and seared areas, or with greyish patches that look like thin, crinkled silk. When the process is

7. Corrigan: Edinburgh Med. Jour., 1832, xxxvii, No. 111, 225.
8. Allbutt: Allbutt's Syst. Med.
9. Bruce, Mitchell: Lancet, London, 1911, ii, 69, 141, 205.
10. Schwarz: Centralbl. f. die ges. Therap., 1911, xxix, 225.
11. Breitmann: Berl. klin. Wchnschr., 1911, xlviii, 1763.
12. Goldscheider: Med. Klin., 1912, viii, 471.
13. Chiari: Verhandl. d. Deutsch. path. Gesellsch., 1903, p. 137.
14. Benda: Verhandl. d. Deutsch. path. Gesellsch., 1903, p. 164.
15. Marchand: Verhandl. d. Deutsch. path. Gesellsch., 1903, p. 197.
16. Fahr: Virchows Arch. f. path. Anat., 1904, clxxvii, 508.
17. Herxheimer: Lubarch Ostertag Ergebn. d. allg. Path. u. Path. Anat., 1907, xi, 195.

extensive the wall at points is thinned, or there may be tiny aneurysmal bulgings no bigger than a pea. When the process is widespread, and apparently of long standing, there is an irregular, or diffuse dilatation of the vessel. True saccular aneurysms are common. Not infrequently the changes are marked about the mouths of the branches of the arch. Occasionally this causes distinct narrowing of the innominate or left carotid. Except in the very oldest cases one never sees atheromatous patches containing cholesterin crystals or calcification. When these changes occur they are associated with a typical endarteritis deformans running throughout the length of the aorta. When the process advances to the aortic ring, as it often does, the mouths of the coronary arteries may be partly occluded, or even reduced to a pin-hole point, though the lesion rarely extends far into the coronary arteries themselves. With the involvement of the sinuses of Valsalva, and the aortic ring, there may be pouching of one and distention of the other, so that the circumference of the ring, instead of being 5 to 7 cm. may reach 9 to 11 cm. The aortic flaps likewise become involved, and show a curious thickened and wrinkled appearance, which causes more or less retraction and incompetence, though in certain cases of typical aortic insufficiency, the valves are surprisingly large and pliable, while the aortic ring is widely dilated. To this Corrigan himself called attention. Even below the flaps on the endocardium in some instances there are crescentic lines of greyish thickening.

Microscopically the earliest lesions which may be definitely recognized show that all three of the main coats of the aorta are involved. The adventitia shows small accumulations of small round cells about the vasa vasorum, and the intima of both arteries and veins may be thickened. Minute blood-vessels extend into the media, and are surrounded along their courses by accumulations of plasma cells, small round cells and epithelioid cells. Slight breaks in the elastic tissue are observed in Weigert's stain. The cells of the intima are proliferated and heaped up to form a projection from the inner surface of the vessel.

In the more extensive lesions the perivascular infiltration of the adventitia is very pronounced. The media presents very characteristic areas of coagulation necrosis surrounded and partly infiltrated with plasma cells and small round cells. Giant cells may be encountered. They sometimes contain fragments of elastic tissue. The elastic tissue in special stains is seen to be destroyed, torn and fragmented, and is usually entirely absent in the center of such a patch. The cellular proliferation of the intima is marked. These areas of necrosis, or miliary gummata, may be of considerable size, and in two specimens which I have studied they involved not only the media, but large areas in the adventitia, and even the adjacent heart wall, forming true gummata, which were readily visible macroscopically. There is frequently a sacculated dilatation of the arterial wall which may vary from a depression scarcely perceptible to a well-formed aneurysm of small size.

The third characteristic picture appears to represent a later stage of the process, and shows a scarred, distorted vessel wall, almost unrecognizable as such, with perhaps complete destruction of all three coats of the artery. Small foci of necrosis surrounded by connective tissue, partly vascularized and infiltrated with varying numbers of plasma cells and small round cells take the place of the media, and extend in marked instances both to adventitia and media, while in appropriate stains the curled fragments of elastic tissue may be seen here and there throughout the lesion.

In certain cases we have found but one of these three types or stages of the process, but as a rule two or all of them are seen in different portions of the vessel walls.

Extending from the root of the aorta the process frequently involves the valves of the aortic orifice and the aortic ring itself. The changes in the valves in such cases consist in localized and diffuse infiltrations of small round cells and plasma cells.

RELATION OF SYPHILIS TO AORTITIS

That such lesions are in themselves characteristic, and may readily be recognized, is granted by most observers, but that they are always and exclusively due to syphilis is questioned still by many. Evidence is accumulating, however, to show that syphilis is certainly the commonest, if not the exclusive cause. The statistical studies of Marchand, Benda, Herxheimer and Fahr, have been mentioned, and the subject has been collectively reviewed recently by Eich.[18] There is general agreement as to the frequency of a history, or other evidence of syphilis in cases showing this type of aortitis.

More direct evidence was brought forward by Reuter[19] in 1906, who described spirochetes in the walls of an aorta affected by this gummatous process. His observation has been confirmed by Schmorl,[20] Benda[21] and by Wright,[22] who was able to demonstrate spirochetes, often in enormous numbers, in all of five cases of mesaortitis. From the results of some studies which I have made, and which Dr. Jean V. Cooke undertook at the Pennsylvania Hospital, the presence of spirochetes in these lesions, as might be expected, cannot by any means be constantly demonstrated with Levaditi stains. Portions of the aorta from seven cases of typical syphilitic aortitis, all of which during life had given a positive Wassermann reaction, were stained by the Levaditi method and searched carefully. In three of these, spiral organisms were found in moderate numbers, sparsely scattered through the thickened intima and underlying portions of the diseased vessel wall. That these organisms are *Treponema pallidum* seems almost certain, though actual proof of such by culture from the arterial lesions, a most difficult task, or direct inoculation into animals, has not as yet been accomplished.

Vanzetti,[23] on the other hand, has claimed to produce an arterial lesion in rabbits which simulated syphilitic aortitis in man by the inoculation of bits of syphilitic rabbits' testicles into the sheath of the carotid artery. In from twenty to forty-one days the syphiloma develops about the wall of the vessels. Spirochetes are found only in the adventitia at the seat of inoculation. Though his pictures and descriptions do not convince one that the experimental lesion corresponds precisely with the aortic lesion in man, yet his observation that the first alteration in the vessel wall after perivascular inoculation is a proliferation of intima cells, is of much interest in connection with the histogenesis of the disease in

18. Eich: Frankfurter Ztschr. f. Pathol., 1911, vii, 373.

19. Reuter: München. med. Wchnschr., 1906, liii, 10, 778; Ztschr. f. Hyg. u. Infektionskr., 1906, liv, 49.

20. Schmorl: München. med. Wchnschr., 1907, liv, 188.

21. Benda: Berl. klin. Wchnschr., 1906, xliii, 989.

22. Wright: Boston Med. and Surg. Jour., 1909, clx, 539.

23. Vanzetti: Tr. First Internat. Cong. Path., Torino, October, 1911, p. 171.

the human artery, where the lesions in the media are usually attended by a proliferation of the cells of the intima.

It remains to be seen, however, whether any other infectious agent may produce the same lesion. Klotz[24] has described alterations in the aorta in cases of rheumatic fever in children which bear some likeness to those ascribed to syphilis. In any such studies it is of the utmost importance to exclude the possibility of congenital syphilis, for, as Klotz[24] himself has shown, lesions practically the same as syphilitic aortitis in the acquired disease may be found in infants the subject of congenital syphilis. Wiesner[25] and Rach and Wiesner[26] have paid considerable attention to this subject, and have found changes in 59 per cent. of the syphilitic fetuses examined. These observations have been confirmed by Bruhns[27] and recently by Rebaudi,[28] who, in five cases, was able to demonstrate spirochetes scattered through the aortic lesion. Rach and Wiesner state that spirochetes were not once found in any of seven cases. These observations afford, besides, strong support to the idea that the disease in adults is due to syphilis.

To the above evidence of the syphilitic nature of this process must be added the valuable results obtained from the use of the Wassermann reaction. Eich, who perhaps has had the largest series of cases controlled by autopsies, obtained a positive Wassermann reaction in 81.8 per cent. of forty-four cases that showed characteristic syphilitic aortitis at autopsy. His technic may be criticised, however, since in a number of instances he employed post-mortem blood. Pearce[29] collected seventy cases of mesaortitis from the literature, in 78.5 per cent. of which the Wassermann reaction was positive.

A question of extreme importance is to determine the time at which the aorta becomes infected. It is known that syphilis during the late primary stage becomes a general septicemia, and in certain cases during this period it is possible to demonstrate spirochetes in the circulating blood (Fruhwald,[30] Uhlenhuth and Mulzer[31]). Following this general invasion of the body the spirochetes lodge in different organs and tissues, spreading by way of the lymphatics; and it is highly probable that the infection of such organs as the aorta, the nervous system and the liver takes place at this period. For some reason, as yet unexplained, the root of the aorta and ascending arch seem to be one of the sites of predilection for the organism. Whether or not there are changes in or about the aorta

24. Klotz: Jour. Pathol. and Bacteriol., 1907, xii, 11.
25. Wiesner: Centralbl. f. Path. u. path. Anat., 1905, xvi, 822.
26. Rach and Wiesner: Wien. klin. Wchnschr., 1907, xx, 521.
27. Bruhns: Deutsch. med. Wchnschr., 1906, No. 19.
28. Rebaudi: Monatschr. f. Geburtsh. u. Gynäk., 1912, xxxv, 681.
29. Pearce: The Archives Int. Med., 1910, vi, 478.
30. Fruhwald: Wien. klin. Wchnschr., 1912, xxv, 584.
31. Uhlenhuth and Mulzer: Berl. klin. Wchnschr., 1912, xlix, 152.

during the secondary stage is a question which at present must be left undecided, but it is quite certain that the results of the invasion of the aorta may become manifest soon after the primary infection. Indeed, in the secondary stage of syphilis there may be certain symptoms and signs referable to the cardiovascular system. Fournier mentions palpitation, arhythmia and tachycardia, but as they occur chiefly in women he ascribes them to functional disorders of the nervous system. Grassmann,[32] in his study of the cardiovascular system of 288 cases of secondary syphilis, states that in 85 per cent. there were disturbances in the rate or rhythm of the pulse, while in 40 per cent. accidental cardiac murmurs usually with dilatation of the heart occurred. Though syphilitic aortitis with its complications—aortic insufficiency, aneurysm, dilatation of the arch and angina pectoris—are usually referred to as late or even parasyphilitic and metasyphilitic affections, there are instances on record in which these conditions have appeared shortly after infection. Harlow Brooks[33] mentions one case in which the perforation of an aneurysm took place before the secondary rash had fully appeared, and another in which a serious aortic lesion, sufficient to cause death, developed within six months of infection. Liek,[34] too, describes a most interesting example in a young man 26 years of age, who developed within seven months after contracting a chancre, dilatation of the aorta visible by *x*-ray. There were mild anginoid symptoms. Two of my patients died from the effects of syphilitic aortitis four years after the development of a chancre, and such instances are not excessively rare. It seems possible, therefore, that even when the effects of the infection do not make themselves apparent for many years, the actual invasion of the aorta may take place during the secondary stage.

CHIEF SIGNS AND SYMPTOMS

Early in the disease, no doubt, the involvement of a small portion of the aorta may be of slight immediate significance, but with the extension of the process, there result four grave conditions—diffuse dilatation of the arch, aneurysm, aortic insufficiency and angina pectoris. I have been particularly interested in the association of aortic insufficiency with syphilitic aortitis. In a study of 76 cases of chronic endocarditis that came to autopsy at the Pennsylvania Hospital,[35] 43 cases gave symptoms and signs during life of aortic insufficiency. In about half, or 21 of these, the mitral valve as well as the aortic valve was diseased, and showed retraction or stenosis, while the individuals were principally children with a history of rheumatic fever. In none of these was syphilitic aortitis

32. Grassmann: Deutsch. Arch. f. klin. Med., 1900, lxviii, 455; 1901, lxvix, 58 and 264.
33. Brooks, Harlow: Med. Rec., New York, 1912, lxxxi, 351.
34. Liek: Fortschr. a. d. Geb. d. Röntgenstrahle, 1911, xvii, 23.
35. Longcope: Jour. Am. Med. Assn., 1910, liv, 118.

present. In the remaining 22 cases, all of which showed involvement of the aortic valves alone, 18, or 81.5 per cent., were associated with syphilitic aortitis.

With the advent of the Wassermann reaction a valuable method was obtained for the study of these cases of cardiovascular disease, and the astonishing frequency with which syphilis appeared as an etiological factor soon became apparent. Citron,[36] in 1908, first reported that of 16 cases of aortic insufficiency, 62.6 per cent. gave a positive Wassermann reaction. In the next year or so came the reports of Danielopolu,[37] Schutze,[38] Collins and Sachs,[39] Clough,[40] Laubry and Parvu,[41] Deneke,[42] Donath,[43] Oigaard,[44] Bruchner and Galesco[45] and Krefting,[46] giving in all, 182 cases of aortic insufficiency, in 135 of which, or in 74.1 per cent., the Wassermann reaction was positive. Pearce, in 1910, collected the statistics of 57 cases of aneurysm, 38 of which gave positive reactions, 70 cases of mesaortitis, 57 of which gave positive reactions, and 214 cases of general arterial sclerosis, 29 of which gave positive reactions. During the years 1909 and 1910, I[47] made Wassermann tests, using the original Wassermann technic, on 12 cases of aneurysm, 11 of which gave positive reactions, and on 47 cases of aortic insufficiency, 35 of which, or 74.4 per cent., gave positive reactions. Of the positive cases, 7 came to autopsy, and all showed typical mesaortitis with involvement of the aortic ring, or of the wall above. In the wall of the aorta of three patients spirochetes were found. The 10 cases of aortic insufficiency which gave negative reactions were, save one, combined with disease of the mitral valve. An autopsy in this one case of pure aortic insufficiency giving a negative Wassermann reaction showed no evidence of syphilitic aortitis. Autopsy on the one case of aneurysm which gave a negative Wassermann reaction showed a definite but old scarred syphilitic aortitis.

Two of the cases of aortic insufficiency, which gave positive Wassermann reactions, were associated with mitral stenosis. One of these came to autopsy, and showed typical syphilitic aortitis involving the aortic leaflets. Spirochetes were present in fair numbers in the wall of the aorta. There was marked irregular thickening and fusing of the mitral leaflets. A nodular, fibrous mass was found on the posterior leaflet. The

36. Citron: Berl. klin. Wchnschr., 1908, xi, 2142.
37. Danielopolu: Compt. rend. Soc. de biol., 1908, lxiv, 971.
38. Schutze: Deutsch. Ztschr. f. Chir., 1908, xcv, 13.
39. Collins and Sachs: Am. Jour. Med. Sc., 1909, cxxxviii, 344.
40. Clough: Bull. Johns Hopkins Hosp., 1910, xxi, 70.
41. Laubry and Parvu: Compt. rend. Soc. de biol., 1909, lxvi, 750, lxvii, 48.
42. Deneke: Deutsch. med. Wchnschr., 1909, xxxv, 2148.
43. Donath: Berl. klin. Wchnschr., 1909, xlvi, 2015.
44. Oigaard: Arch. de mal. de coeur., 1910, iii, 478.
45. Bruchner and Galesco: Compt. rent. Soc. de biol., 1910, lxviii, 74.
46. Krefting: Deutsch. Med. Wchnschr., 1910, xxxvi, 93.
47. Longcope: Bull. Ayer Clin. Lab., 1910, No. 6, p. 60.

chorda tendineae were thick and looked as though scarred. Spirochetes could not be found in the mitral lesion. Whether the mitral stenosis was a result of the syphilitic process, or caused by some acute infection, such as rheumatic fever, of which there was no history, could not be determined, but it is evident that mitral stenosis may exist with syphilitic aortitis.

To control the above observations Wassermann reactions were performed on fifty cases, including various types of mitral disease, cardiac hypertrophy secondary to nephritis, and general arterial sclerosis. In the entire series only three positive Wassermann reactions were encountered, two in cases of chronic nephritis with arteriosclerosis, and one in a case of mitral stenosis and insufficiency. This proportion is at least what one might expect in any material collected among adults in a large general hospital.

Since the completion of these studies still other confirmatory reports have been made by Grau,[48] Orkin,[49] Ledermann,[50] Bie,[51] Fiessinger,[52] Jacobeus,[53] Comesatti,[54] Hirtz and Braun,[55] Weintraud,[56] Cummer and Dexter,[57] Goldscheider[58] and others. The percentage of positive Wassermann reactions are variously given: for general cardiovascular diseases from 25 per cent. to 68 per cent.; for aortic insufficiency from 75 per cent. to 100 per cent.; for aneurysm from 85 to 95 per cent., and for aortic diseases in general, including aneurysm, diffuse dilatation and angina pectoris, from 75 to 88 per cent.

Wolfsohn[59] has recently found that positive reactions to Noguchi's luetin in cardiac disease are even more frequent than the Wassermann reaction. In 12 cases, including 6 of aortic insufficiency, 4 of aneurysm, and 2 of myocarditis, 11, or 91 per cent., reacted to luetin. The one negative reaction occurred in a case of myocarditis. The Wassermann reaction was positive in but 58.3 per cent.

Even from these rather small statistics, confirming as they do the anatomical studies, it may be seen how extremely common syphilitic aortitis and its complications are, and what a large proportion of serious diseases of the cardiovascular system in adults may be dependent on this

48. Grau: Ztschr. f. klin. Med., 1911, lxxii, 292.
49. Orkin: Berl. klin. Wchnschr., 1912, xlix, 1177.
50. Ledermann: Deutsch. Med. Wchnschr., 1912, xxxviii, 1038.
51. Bie: Ugesk. f. Laeger, 1911, lxxiii, No. 11; Abstr. in Jour. Am. Med. Assn., 1911, lvi, 1158.
52. Fiessinger: Bull. de l'Acad. de méd., 1911, series 3, lxvi, 135.
53. Jacobeus: Deutsch. Arch. f. klin. Med., 1911, cii, 44.
54. Comesatti: Riv. crit. di clin. med., 1911, xii, 561 and 581.
55. Hirtz and Braun: Bull. et mém. Soc. d. hôp., 1911, series 3, xxxi, 363.
56. Weintraud: Therap. d. Gegenw., 1911, lii, 442.
57. Cummer and Dexter: Jour. Am. Med. Assn., 1912, lix, 419.
58. Goldscheider: Med. Klin., 1912, viii, 471.
59. Wolfsohn: Bull. Johns Hopkins Hosp., 1912, xxiii, 223.

disease. It is evident that most aneurysms of the arch of the aorta, the majority of cases of aortic insufficiency in adults, uncomplicated by mitral disease, many cases of angina pectoris, particularly in individuals under 50 years of age, and a large proportion of cases of dilatation of the aorta are only incidents in the development and progress of syphilitic aortitis, and unfortunately in many instances are the first signs that attract our attention to the disease. But it is most important that we should not lose sight of the main and underlying process, and serious as the complications are, our attention should be directed to a study of the diseased aorta rather than to the late manifestations.

CLINICAL PICTURE

The clinical picture, it is true, is made up principally of the symptoms and signs which accompany these end results, but there are certain features common to all types of the disease the explanation for which is somewhat difficult to give, but which may repay further study. To many clinicians the disease has been familiar for years. Aside from the well-known descriptions given by Hurhard, Dieulafoy, Gallavardin, Fournier and Allbutt†, the symptomatology and diagnosis have recently been discussed by Mitchell Bruce and Osler[60] in their Lumleian Lectures, and by Breitmann, Schwarz, Goldscheider, Bruhns,[61] Oigaard,[62] Grau, Fiessinger, Orkin and Cummers and Dexter.

The 63 cases on which this study is based, include 43 cases of aortic insufficiency, 4 of which were combined with aneurysm, 8 cases of aneurysm alone, and 12 cases of aortitis associated with dilatation of the arch, myocarditis, angina pectoris, or a combination of these conditions. The diagnosis was made or confirmed at autopsy in 29 cases; in 10 of these the Wassermann reaction was performed during life and found positive. In the remaining 34 cases the Wassermann was positive. For the Wassermann reactions in 13 cases which were studied at the Presbyterian Hospital, I am indebted to Dr. Albert Lamb. In making these tests the Noguchi modification was used. In all the other cases I employed the original Wassermann technic.

AGE INCIDENCE

Most authors have mentioned the fact that these cardiovascular changes due to syphilis are met with in comparatively young people. In Bie's statistics the average age at which the symptoms of syphilitic aortitis developed was 42; for aneurysm 50, and for myocardial disease 52. Mitchell Bruce, in a study of 70 odd cases gives the average age at

†Allbutt: Lancet, 1903, ii, 139; Brit. Med. Jour., 1906, i, 5.
60. Osler: Lancet, London, March 12 and 26 and April 9, 1910.
61. Bruhns: Berl. klin. Wchnschr., 1906, xliii, 513.
62. Oigaard: Ztschr. f. klin. Med., 1911, lxxiii, 440.

which the first manifestations occurred as 49. Of Cummers and Dexter's 27 patients, 85 per cent. were between the ages of 35 and 55 years. In my own series, the majority of the patients were young, as may be seen in the following table:

Age	Cases	Per cent.	Age	Cases	Per cent.
20-30	19	30.1	20-40	32	50.7
31-40	13	20.6	20-50	51	80.9
41-50	19	30.1			
51-60	7	11.1			
61	5	7.9			
	63				

Over one-half of these patients were less than 40 years of age, and 80.9 per cent. under 50. Almost a third of the patients were under 30 years of age. The youngest patient was a colored woman of 22. At autopsy there was extensive syphilitic aortitis. There were three other patients under 25, all of which came to autopsy and showed extensive syphilitic aortitis. The oldest patient was 68. As a rule, the aneurysms occurred in the older subjects. Except for one case in which a small aneurysm was found at autopsy in a woman of 26, most of the individuals, 10 out of 13, were over 40, and 6 were over 50.

Of the 63 cases, 51 were men; 25, or about half, were negroes. Of the 12 women, 10 were negroes.

It has been generally assumed that the symptoms of syphilitic aortitis develop as a late event in the disease. In Bruce's statistics the average latent period between the time of infection and the onset of symptoms was 25 years, in Cummer and Dexter's report 17.2 years. Bruce gives the minimum period as 5 years, the maximum as 54. Bie points out that symptoms in these cases make their appearance about 15 years later than they do in rheumatic fever. Owing to the difficulty in obtaining an accurate history I could determine such data in but 23 cases. Roughly, the average latent period was 16.4 years, very nearly that given by Cummer and Dexter. The shortest period was 3 years, and there were 4 other cases under 5 years. The longest latent period was 35 years. Bearing on this question of latency is an interesting report by Biermann.[63] Reference has already been made to the changes found in the aorta of congenital syphilitics, and Biermann has recently described a case of congenital syphilis in a girl of 19, who showed dilatation of the aorta with fever. He considers this as an instance of congenital syphilitic aortitis. Wentworth,[64] too, has recently reported a series of Wassermann tests in children among which were five cases of congenital heart disease, two of which gave positive reactions. It is evident that there may be

63. Biermann: Deutsch. med. Wchnschr., 1911, xxxvii, 1157.
64. Wentworth: Am. Jour. Dis. Child., 1912, iii, 363.

syphilitic disease of the aorta which remains latent and gives no symptoms over long periods of time.

It is impossible to determine whether any secondary factors acted as predisposing causes in the development of the aortitis. Many of the men were hard working. A history of alcohol, or abuse of tobacco, was not particularly striking. One patient had tabes dorsalis. The frequent association of tabes and aortic disease is well known, and the question has been thoroughly discussed by Heitz.[65]

SYMPTOMS

The symptoms which have attracted the attention of every one who has written on the subject are pain, dyspnea, often on slight exertion, palpitation and tachycardia. Pain was a prominent symptom in 60 per cent. of Bruce's cases. In one-half it was precordial, in the other half anginal in character. Dyspnea occurred in 60 per cent., palpitation in 67.5 per cent. In my series pain of one sort or another, excluding the continuous cervicobrachial neuralgic pains of aneurysm, occurred in 42 cases, or 66.6 per cent.; dyspnea in 49, or 77.7 per cent. Palpitation and tachycardia were less frequent.

Pain is an interesting symptom not only because it is so characteristic of this type of cardiovascular disease, but on account of its relationship to the state of angina pectoris, the true nature of which is still so imperfectly understood. It is frequently the first symptom (29 cases), and alone or in combination with dyspnea of various types may be the only symptom for long periods (9 cases). Osler[66] has called attention to the anginoid pain which may precede the appearance of an aneurysm. The cervicobrachial neuralgia, so common in aneurysm, I have not included in this description. The pain is of various kinds. In the majority of cases the patient complains either of a constant or intermittent dull pain beneath the sternum. Sometimes it is described as a painful constriction or oppression, sometimes as a "gripping sensation that comes up from the stomach, and catches at the heart or throat." Mild at first, these disagreeable sensations usually increase in severity, and intermittent attacks become more frequent. In a majority of cases the pains are made worse by exercise. Beginning with mild attacks the patient may one day have a typical paroxysm of angina pectoris accompanied by fear of impending death, and with radiation of pain to the neck, left shoulder, or down the left arm. Rarely the disease starts with severe, typical angina pectoris. Characteristic attacks of angina pectoris occurred in eight of my patients, five of whom had aortic insufficiency. Two patients dropped dead.

65. Heitz: Les nerfs du coeur chez les tabétiques, Paris, 1903.
66. Osler: Med. Chron., May, 1906.

Although the attacks of angina may be free from any disturbances in respiration, very frequently they are closely associated with distinct changes. Occasionally the patient stops breathing in full inspiration; more often there is dyspnea of moderate grade, or attacks of paroxysmal dyspnea, to be described later, accompany the pain so that it is sometimes difficult to distinguish the two. Dyspnea is frequently associated with the milder substernal pain. In the attacks of angina which are free from dyspnea there may be a sharp rise in blood-pressure; in one case from 110 systolic to 170 systolic.

The dyspnea itself is a symptom of the greatest interest, and in one of its forms seems to be highly characteristic of the disease. In the majority of cases there is early dyspnea on slight exertion. In thirty-one cases, or about half, it was one of the first, if not the first symptom. In some cases this slight shortness of breath gradually becomes worse, especially when aortic insufficiency supervenes, until the patient finally shows the constant respiratory difficulty common in broken cardiac compensation. In a second group of cases the dyspnea assumes another and more interesting, though most distressing form. In this group it is paroxysmal in nature, coming on in attacks of five to fifteen minutes' duration. Such attacks were present in nine of my patients, all of whom had aortic regurgitation. These paroxysms may be absolutely the first symptom (seven cases). They vary greatly in number, from two to three during the entire course of the disease, to four or five a day over periods of months. In two cases they occurred daily for almost a year. Though this phenomenon is most common when aortic insufficiency is present, it is seen in cases in which signs of cardiac decompensation do not develop for months, and in one case which is now under observation there have never been signs of decompensation, unless, indeed, these attacks are considered as such. Sometimes the attack is brought on only by exertion, but in the majority of cases the paroxysm is absolutely independent of exercise, and not infrequently strikes the patient like a thunderbolt, often while he is asleep at night. Between attacks he is usually able to perform his daily duties. I have observed a number of such attacks in different individuals, and the following notes made at the bedside will give some idea of their nature.

"Suddenly during rounds at 10:40 a. m. the patient showed signs of great distress. He sat up in bed, and gave a sharp agonized cry for help. Going immediately to the bedside he was found sitting up, leaning forward with a pained, anxious expression, and showing the most marked dyspnea. He implored us to relieve him of his distress, but talked quite intelligently throughout the attack, and said there was no actual pain, but terrific difficulty in getting his breath. The supraclavicular spaces were retracted during inspiration, the chest moved scarcely at all, while the respiratory excursions of the abdomen were extreme. Respiration was rapid, and though inspiration seemed difficult, expiration was accomplished with the greatest effort and exertion, and was comparatively much

prolonged. The pulse was 128. The chest was hyperresonant, and on auscultation were heard diffusely scattered sibilant and occasional crackling râles. About the height of the attack the patient began to sweat about the head and face. At this time too, he began to cough, and expectorated a small quantity of thick blood-stained mucus. At 10:45 amyl nitrite was applied; at 10:53 1/100 gr. nitroglycerin hypodermatically. During the coughing spell he asked to hang his legs over the side of the bed. He did so, and at 11:05 the feeling of distress disappeared rapidly. The respirations continued, however, to be rapid, and at 11:20, fifteen minutes later, were 35, pulse 108. During the attack the blood-pressure rose from 200 S., 70 diastolic, to 247 S., 70 diastolic, to fall in eleven minutes to 178 S., 60 diastolic. At the end of the attack the râles had disappeared over the chest."

Such is the character of these paroxysms; short, lasting often from ten to fifteen minutes, but leaving the patient exhausted for an hour or two afterwards; agonizing, terrifying both to the patient and to the individual who sees him, usually accompanied by an increased pulse-rate, and a rise in blood-pressure that falls rapidly at the subsidence of the attack.

In the attack just described there was no pain, but in some cases there is pain, often excruciating, starting in the substernal region and radiating to the neck, left shoulder and down the left arm. In one case the pain radiated down the right arm. In the severest cases there is usually a cry for help at the start. Some patients remain almost immobile during the paroxyms, others wave their hands and arms about frantically. There is never an attempt to get out of bed or rush to the window. Often there is the fear of impending death. Nitroglycerin has seemed to bring relief.

In the instances that I have watched the dyspnea was distinctly expiratory. The patient could not empty his lungs. During the attacks the chest became emphysematous, and auscultation revealed piping and occasional crackling râles. There was sweating and cyanosis. The attack ended with the expectoration of a little bloody mucus. The agony during some of these attacks is terrific. One patient in whom the dyspnea was associated with angina cut his throat. In two cases the attack itself was fatal.

The condition is very well known. Osler describes it most accurately, and speaks of the condition as one nearly allied to angina—angina of pulmonary type. Oigaard refers to it as *Luft-Hunger,* to the French it has long been familiar and Huchard terms it paroxysmal dyspnea; by the older authors it is referred to as cardiac asthma, and by some it has probably been considered as acute pulmonary edema. Breitmann calls particular attention to its significance in these cases. Though Huchard as well as many others would definitely exclude these cases from the category of angina pectoris, it is certainly difficult to say in some instances whether the patient is suffering from an attack of angina pectoris with severe respiratory symptoms, or whether he is suffering with paroxysmal

dyspnea with pain, for the attacks vary in different individuals from purely respiratory phenomenon, uninfluenced by exertion, and free from pain, to attacks in which the pain predominates, and in which the paroxysms are definitely associated with exertion. The attacks in their characteristic form simulate very closely a transient severe asthma, an extreme expiratory dyspnea with acute emphysema, and suggest very strongly that the direct cause of the dyspnea is bronchiospasm. The possible explanation of the phenomenon can best be discussed when we come to consider the effect of treatment on these symptoms of pain and respiratory distress.

Palpitation is of fairly common occurrence, and may occur early; with this there is sometimes tachycardia. With the development of cardiac insufficiency in the cases of aortic regurgitation or of myocarditis, there naturally ensue the symptoms common to decompensation.

If aneurysm exists the special pressure symptoms dependent on the tumor make their appearance. In eleven of the twelve cases of aneurysm there was pain, usually constant, in the chest, left shoulder, neck and left arm.

As Allbutt has long pointed out, however, these symptoms described above appear most frequently when the sigmoid region is involved, and this has been particularly true in my series. I have also noted that in the younger patients, pain and paroxysmal dyspnea have been most frequent. In seven patients over 50, who had aortic insufficiency, pain was entirely absent in two and very slight in three, the picture in these five cases being almost entirely that of gradual cardiac decompensation. In the remaining two cases there was severe pain and paroxysms of dyspnea.

Finally, it is necessary to mention the possible relationship between the syphilitic aortitis, and certain unexplained fevers in these cases. To this Popoff[67] has recently called attention. He reports three cases of aortic insufficiency with syphilitic aortitis in which there was an unexplained fever that disappeared rapidly after the administration of antisyphilitic treatment. In Biermann's case of congenital syphilitic aortitis there was fever. Though it is not uncommon to see slight fever or abnormally great variations in temperature in cases of aneurysm and aortic insufficiency with syphilitic aortitis, particularly just after admission to the hospital, it is difficult to exclude in such instances the presence of a slight bronchitis as a cause for the increased temperature. It is interesting, however, to note the effect of treatment on this temperature. In one of my cases of aortic insufficiency, there was a mild unexplained fever reaching at times 101 F., which lasted for eleven days, but disappeared promptly after the first dose of salvarsan. In a second case, fever played a very prominent part in the picture.

67. Popoff: Ztschr. f. klin. Med., 1912, lxxv, 506.

CASE REPORT

A married woman aged 53 was admitted to the Presbyterian Hospital May 6, 1912, complaining of general weakness. She had never been sick before. She had not had any children; the menopause had occurred four months previously. For six months she had been feeling badly, weak, and was losing weight. There had been no edema, no pain, no dyspnea, no cough. For six to eight weeks there had been fever with night-sweats. She was an under-nourished, rather pale woman. In both conjunctivae there were small petechiae. The teeth were bad. The lungs were negative to examination. There was some enlargement of the heart, with a faint systolic murmur at the apex, and a double murmur at the base. The liver was palpable two fingers below the costal margin. The spleen could not be felt. There was no edema. The Widal was negative. Leukocytes 8,000; hemoglobin 75 per cent.; red blood-corpuscles 4,400,000; 5/11, von Pirquet negative; 5/13, Wassermann +++ (Noguchi). From time to time a few petechiae were noted over shoulders and back. Blood-cultures made 5/14 and 5/28 gave no growth.

The course of the fever with the injections of salvarsan and Wassermann reactions are shown on the accompanying chart (Fig. 1).

June 13 the patient left the hospital much improved. As the fever did not entirely cease she consulted a physician, who treated her with intramuscular injections of salicylate of mercury. By the middle of July she had improved still further, and was entirely fever-free. She remained afebrile, but in September, 1912, suffered a severe break in compensation, from which she died Oct. 18, 1912.

It is of course possible to have an acute bacterial endocarditis or chronic infective process engrafted on a syphilitic aortitis, and two such cases I have followed to autopsy. It is difficult to exclude in this case such a cause for the fever, especially since there were petechiae, a feature so characteristic of subacute or chronic infective endocarditis. Blood-cultures, however, were constantly negative, while the complete disappearance of fever over a period of months would be unusual in infective endocarditis, unless the process had healed — as far as we know, an exceedingly rare occurrence. The gradual decline of fever and general improvement with the very persistent Wassermann reaction under treatment, together with the complete disappearance of fever with prolonged antisyphilitic treatment, suggest very strongly that the fever in this case was really dependent on the syphilitic infection of the aorta.

The early physical signs, unfortunately, are not numerous, and are sometimes difficult of detection, while the outspoken signs usually occur late in the disease.

The earliest, the most important, and the most constant single sign is a positive Wassermann reaction. It is now generally conceded that a positive Wassermann reaction in syphilis means active infection somewhere in the body (Boas[68]). And here I should like to call attention to the possibility and importance of syphilitic aortitis as a cause for positive Wassermann reactions in so-called latent syphilis. From the frequency with which syphilitic aortitis is found accidentally at autopsy, we know that the infection may be harbored in this situation for years without

68. Boas: Di Wassermann'sche Reaktion, Berlin, 1910.

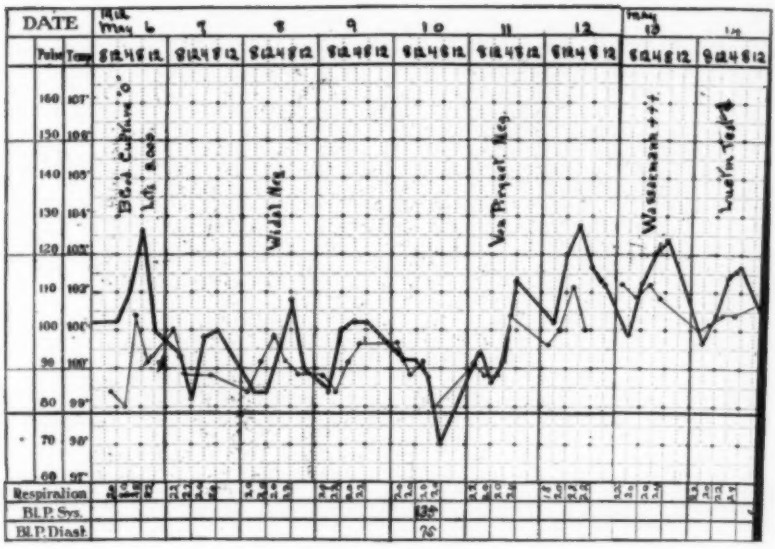

Figure 1.—Part 1.

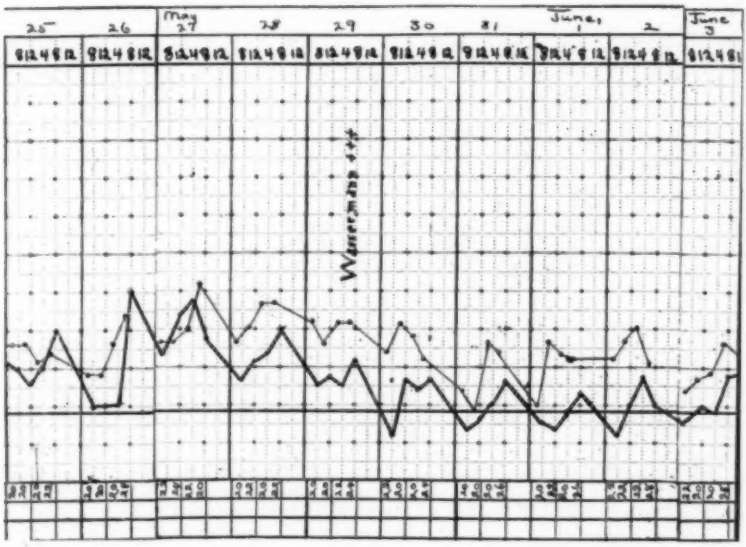

Figure 1.—Part 3.

Fig. 1.—Chart showing fever curve and results of Wassermann test in the

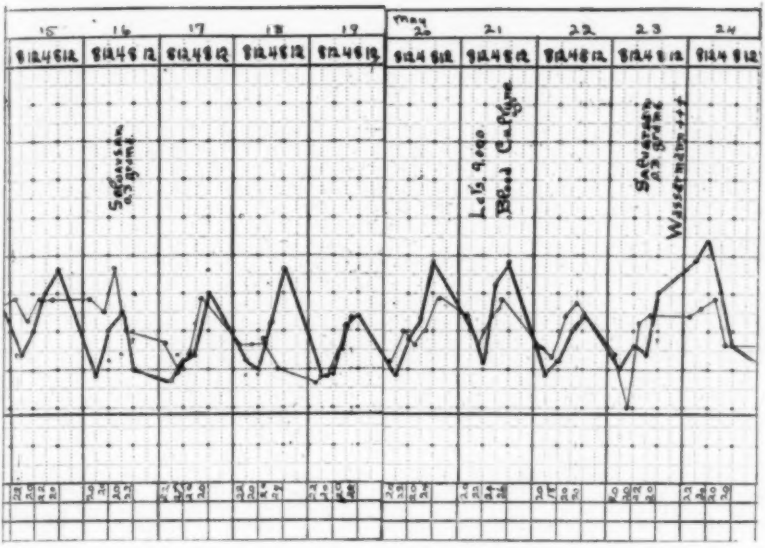

Figure 1.—Part 2.

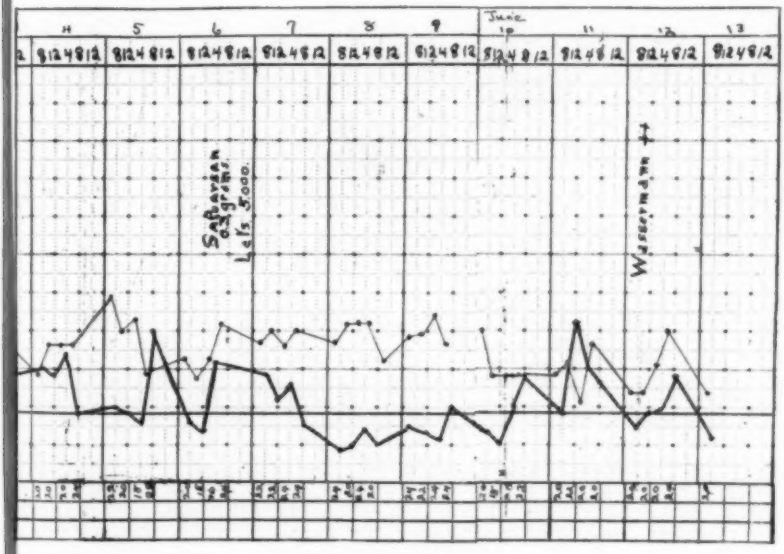

Figure 1.—Part 4.

ase reported by the author. Heavy line = temperature; light line = pulse.

detection during life, and indeed it seems as if the root of the aorta might be one of the chief situations in which the infection may lurk. Eich, in his pathological study of 63 cases of syphilitic aortitis, states that in 36, or over half, there were neither signs nor symptoms of the disease during life. One must nevertheless take exception to this statement, for in 9 cases the patients suffered from cardiovascular diseases. Excluding these 9 cases, however, there are still 27, or 42.8 per cent., in which the infection of the aorta was discovered by accident. In 24 out of 30 cases the Wassermann reaction was positive with post-mortem blood. I have now seen a number of cases in which a patch of syphilitic aortitis, wholly unsuspected until autopsy, was the only cause which could be found to explain a positive Wassermann reaction during life. This question, of course, needs further investigation before any definite statement can be made, but certainly the association is very striking, and probably very frequent. It is therefore of the utmost importance to investigate the cardiovascular system with the greatest care in all cases of so-called latent syphilis that give positive Wassermann reactions. The same statement naturally applies to the nervous system.

Next to the importance of the Wassermann reaction is the condition of the aorta itself. In a certain proportion of cases, but not in all, the lesion leads to a dilatation of the ascending aorta and arch. Dilatation is most common in the older and advanced cases. In 8 of our 35 autopsies there was no dilatation of the aorta. In two cases in which the patients are still living, *x*-ray examination showed no dilatation. In 25 cases, however, either the *x*-ray or autopsy disclosed a dilatation of varying grade. This may be uniform or somewhat irregular. For a complete recent discussion of the symptomatology and diagnosis of aortic dilatation one should refer to McCrae's[69] excellent article. One of the most prominent signs is an abnormal pulsation in the subclavian and carotid arteries with an impulse in the episternal notch. In marked instances there is a heave beneath the manubrium or pulsation in the first and second interspaces, usually to the right of the sternum, but sometimes to the left. The veins of the neck are often prominent. In a few instances I have noted a line of dilated veins extending in a semicircle from the first to the third or fourth ribs, and to the right of the sternum.

On palpation a pulsation is often felt in the episternal notch, occasionally a heave and sometimes even a thrill over the manubrium. Percussion gives dulness over the sternum extending either to the right or left of the manubrium in the first and second interspaces. Auscultation very frequently reveals a systolic murmur at the aortic cartilage. The second sound is sharp, ringing, and has the bell-like quality so aptly emphasized by McCrae. This may be present, even in cases of aortic

69. McCrae: Am. Jour. Med. Sc., 1910, cxl, 469.

insufficiency, when the heart sound is accompanied or followed by a diastolic murmur. These sounds are frequently well transmitted over the upper sternal dulness, and beneath the clavicles, or even into the vessels of the neck. Pressure effects are sometimes noted. There may be a capillary and collapsing pulse even in the absence of an aortic insufficiency.

Of all the methods of physical diagnosis, however, to determine whether or not dilatation exists, the *x*-ray is the most valuable. The orthodiagraph, as pointed out by Vaquez,[70] gives undoubtedly a more accurate picture than the skiagram or fluoroscopic examination, but we

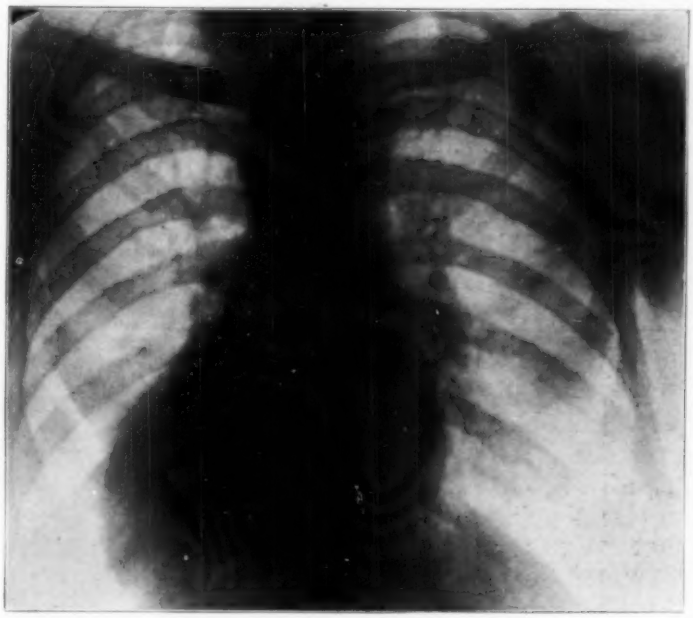

Fig. 2.—Case 15. Angina pectoris and aortic insufficiency. Practically no dilatation.

have been obliged to confine ourselves to the latter methods. Fluoroscopy seems indispensable. Examinations have been made with the patient in the prone position, and lately it has seemed useful to examine the patient first with the screen on the chest, and then on the back. In the latter position, when the patient lies on his face, the shadow of the heart is not very clear, but the outline of the arch and descending aorta is very distinct, and can be studied with much advantage. The details of the changes in the size and shape of the aortic shadow when dilatation exists

70. Vaquez: Arch. d'électricité med., 1911, xii, 561.

have been well discussed by Vaquez, and indeed are familiar. The shadow of the normal aorta as seen on the fluoroscopic screen, or in the skiagram lies in its first portion behind the sternum, but at the arch where it curves rather sharply backwards and to the left, there is a well defined rounded knob, seen to the left of the sternum and opposite the second dorsal vertebra. According to the age of the patient and position of the heart, the shadow may show certain slight variations, but none which can be confounded with definite dilatation (Fig. 2).

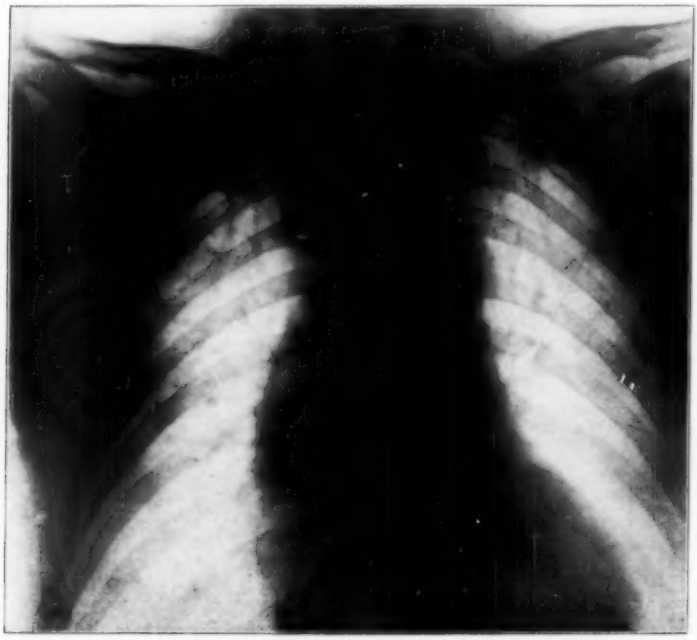

Fig. 3.—Case 14. Angina pectoris, systolic murmur at base and diffuse dilatation of aorta.

The commonest changes that I have observed in dilatation are as follows:

First, the aortic shadow as it ascends from the heart shadow is widened so that it projects in a curved line beyond the sternum and reaches to or extends beyond the curved right border of the heart (Fig. 3). In most instances the outer shadow is regular, but it may show slight protrusions or bulgings. To the left the normal shadow is broadened. There may, too, be localized irregularities on this outline. In a second group there are alterations of a more or less prominent character in the shadow of the aortic knob, but since this represents the arch, it is

unaffected unless the dilatation reaches that far. The commonest abnormality which has been observed is a general enlargement with loss of the well-defined knob shape (Fig. 4), instead of which there is a crescentic curve towards the left. In other cases the knob may be enlarged, and its form more prominent than normal (Fig. 5). Finally, in a third group the aortic shadow appears more or less as a truncated cone with rounded apex and broad base resting on and fusing with the cardiac shadow. In such instances the normal aortic knob is obscured.

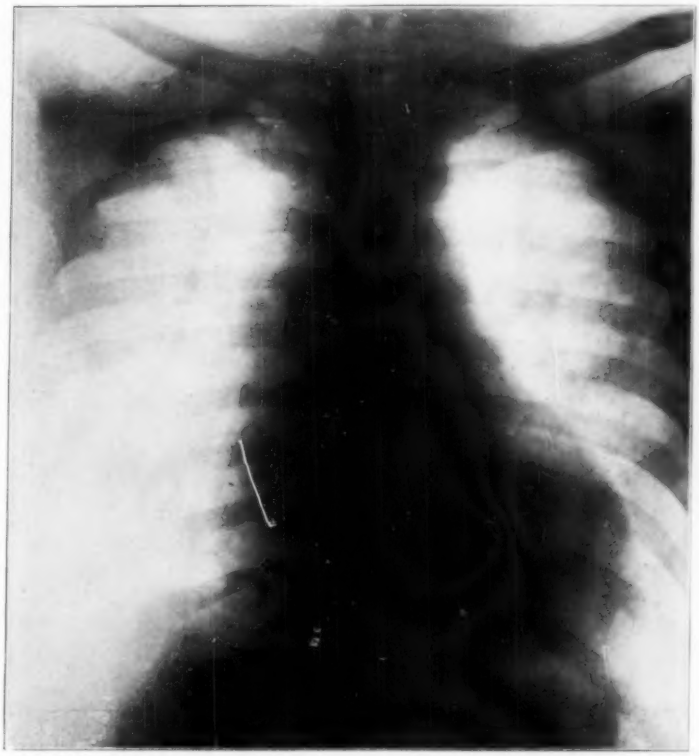

Fig. 4.—Case 10. Aortic insufficiency, paroxysmal dyspnea and diffuse cardiac dilatation.

In any instance, but best shown in Figure 3, there may be above the aortic shadow a pyramidal-shaped shadow with base upwards, and beneath the clavicles. This often corresponds to dulness which is obtained beneath the sternal ends of the clavicle. Comparing this shadow with the appearance of the structures in the superior mediastinum at autopsy, it seems to represent the dilated great arteries as they arise from the arch, and course

upwards. In almost any case, but not frequently, the heart may assume a position more nearly horizontal than normal.

Though syphilitic aortitis commonly results in more or less dilatation of the aorta, it is not of course the only cause, so that diffuse dilatation does not in itself form sufficient basis for a diagnosis. In aortic insufficiency following rheumatic fever there may be marked permanent dilatation without the presence of macroscopic lesions in the aorta, save perhaps a thinning of its walls.

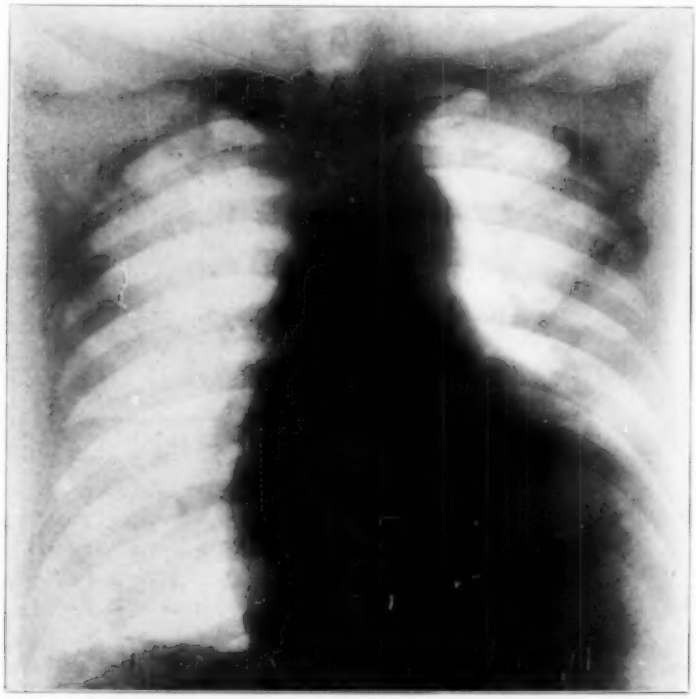

Fig. 5.—Case 11. Syphilitic aortitis; dilatation of aorta; prominence of aortic knob.

The importance of the presence of aortic insufficiency and aneurysm have been sufficiently emphasized; unfortunately they appear as a rule late in the disease.

Some increase in the size of the heart is usually found in all cases whether aortic insufficiency exists or not. With the marked enlargements there are as a rule loud systolic murmurs at the apex. In one case, however, there existed only a presystolic gallop rhythm.

The pulse in the majority of instances is regular, and we have not noted any characteristic qualities, though in one instance a markedly collapsing pulse and capillary pulse existed without any other signs of aortic insufficiency. Occasionally the patches of aortitis, which not infrequently are situated about the mouths of the great vessels, become sufficiently extensive to narrow their lumen, or even to occlude them, in which event the pulse in the two radials or carotids show inequalities in size and force. In one case the pulse in the left common carotid was completely obliterated. Occlusion of the opening of the vessel was found at autopsy.

The prognosis, at least in cases which are seen in general hospitals, is bad. In 24 fatal cases in Bruce's series the average duration of life was 5.2 years. In my series there were 38 fatal cases. Of these, 4 patients succumbed to acute infections not directly connected with the aortitis. In the remaining 34, death took place in 23, or in 67.6 per cent., within a year and a half of the onset of symptoms, and in 9, or 26.4 per cent., within six months of onset of symptoms. The most rapid culmination took place in one case in a few weeks, 2 patients died within two months; the most prolonged case lasted about six years. Of the 25 patients who are known, or are supposed to be living, the disease has existed in 9 for two years, in 4 for three, in 4 for four, in 1 for five and in 4 for six years. Of the 38 fatal cases, 8 patients died suddenly in an attack of angina pectoris, or paroxysmal dyspnea, 3 died of acute infectious diseases, and the remainder succumbed to cardiac failure.

In some cases, particularly the advanced ones, the diagnosis is made with ease and certainty, but in others with the greatest difficulty. The commonest symptoms and signs are substernal pain, or angina pectoris; slight dyspnea on exertion, or attacks of paroxysmal dyspnea, evidence of a dilated aorta, and enlargement of the heart. A combination of any, or all of these with aortic insufficiency in a man or woman about or below middle life, is characteristic, while a positive Wassermann reaction assures the diagnosis in practically every instance. The mere presence of an aneurysm of the arch or root of the aorta presupposes in almost every instance syphilitic aortitis.

The history of severe rheumatic fever in a young man with aortic insufficiency, who gives a positive Wassermann reaction, may well lead to confusion, and unless pain or paroxysmal dyspnea be present, it would seem well-nigh impossible to come to any conclusion as to the etiology of the aortic lesion. I have seen two such cases in which an exact diagnosis could not be made. Since the Wassermann reaction is one of the most constant evidences, it may, and indeed should, be the first indication to put the physician on his guard, and suggest in cases of so-called latent syphilis the most careful examination of the cardiovascular system.

TABLE OF COLLECTED CASES OF SYPHILITIC AORTITIS

No.	Name	Admitted	Sex	Color	Ages	Syphilis	Duration of Illness	Symptoms
1	M	6/16/11	F	C	39	?	1 year	Aching in chest and back; later spells of shortness of breath; lately edema.
2	H	4/14/11	M	C	49	Denies	16 mos.	Began with dyspnea on exertion, slight cough, oppression in chest; four days before admission sudden severe pain in chest, violent dyspnea, cough, fulness in stomach, edema.
3	B	4/13/11	M	C	68	Denies	3 years	Cough, swelling of feet 6 mos., dyspnea, slight pain in chest, blind spells.
4	D	1/17/11	M	W	48	Denies	1 year	Sense of constriction about chest; pain in left side of neck and down left arm; no dyspnea or edema.
5	M	11/28/10	M	W	41	16 years	1 year	Pain in chest and back, severe and constant. Lost 20 lbs. in weight.
6	L	9/13/10	M	C	35	Denies	5 weeks	Attacks of dyspnea and smothering sensation, palpitation, late edema, rapidly worse.
7	Mc	7/29/10	M	W	33	15 years	9 months	Pain in chest, shortness of breath on exertion. Later angina with dyspnea during attack; edema.
8	M	11/25/10	M	C	39	4 years	5 months	Pain in chest, coming on with exertion radiating to left shoulder. No dyspnea. No edema.
9	R	11/11/10	M	C	46	29 years	11 months	Slight dyspnea on exertion; paroxysmal dyspnea with pain; edema of feet for 8 mos.
10	H	10/22/11	M	C	28	Denies	2 months	Paroxysms of dyspnea with sense of constriction in chest. No edema.

TABLE OF COLLECTED CASES OF SYPHILITIC AORTITIS—(Continued)

Diagnosis	Wassermann	Salvarsan	Reaction	Entire Duration of Disease	Remarks
Aortic insufficiency; no dulness over sternum.	6/17+++	6/24, 0.3 gm. intraven.	None	1 yr. 8 mos. Dead	Death, Feb. 12, 1912. No autopsy. Slight imp.; return of symptoms later, with pain.
Aortic insufficiency, cardiac insufficiency, diffuse dilatation of aorta *x*-ray.	4/20+++ 5/24 neg.	4/26, 0.25 gm. intraven. 5/20, 0.3 gm. intraven.	None None	1 yr. 10 mos. Living	Marked improvement. Temporary loss of pain. Able to work again; 6 mos. later decompensation without pain.
Aortic insufficiency, broken cardiac compensation.	4/18+++ 5/24+++ 6/ 7++ 6/21++	4/28, 0.3 gm. intraven. 5/20, 0.3 gm. intraven. 6/10, 0.3 gm. intraven.	None Chill Nausea	3 years + ?	Improvement marked, 5/20, pain in chest gone, 5/26, has pain in chest. Decomp. impr'd on rest and dig. Left hosp. feeling well, pain gone.
Dilatation of aorta (*x*-ray); slight aortic regurgitation, enlarged liver, anginal pain.	1/24+++	2/10, 0.6 gm. intramusc.	Fever	2 yr. 10 mos. +. Living	Much improved. Aug. '12, working hard; feels well.
Dilatation of aorta (*x*-ray). Heart normal; anginal pain.	1/30++ 2/15—	12/ 8, 0.6 gm. intramusc.	Slight	3 yrs. + Living	Greatly imp. Perm. (?). Gained wgt.; Aug. 12, working as fireman.
Aortic insufficiency. Dilatation of aorta, severe broken compensation.	10/14+++	11/14, 0.45 gm. intramusc.	Local	5 months Death	Very slight temporary improvement. Sudden death. Autopsy. Syphilitic aortitis involving aortic valves, pseudolobar pneumonia. Sections of aorta do not differ from other cases.
Aortic insufficiency. Dilatation of aorta (*x*-ray); very slight edema; angina pectoris; S. P. 170; D. 70.	9/16+++	11/21, 0.45 gm. intramusc.	Local	1 yr. Death	Marked temp. imp. Anginal attacks 3-4 times daily before salvarsan. Two wks. after treatm. much better. Sometimes only one attack in 3 or 4 days. By 12/28, recurrence. Suicide. Autopsy: Dilatation of aorta; aortic insufficiency.
Aortic insufficiency; angina pectoris; S. P. 120; D. 80.	11/30+++ 12/21++ 1/10/11++ 2/ 7++	11/30, 0.6 gm. intramusc.	Local	8 mos. Dropped dead	No definite relief from angina. Death, 2/13, 1911.
Aortic insufficiency. Paroxysmal dyspnea with pain. Broken compensation. S. P. 178. D. 90.	11/14+++ 12/21++ 1/10+ 2/28+ 3/ 3— 3/24+ 4/12++	11/16, 0.5 gm. intramusc.	Local	1 yr. 5 mos. Death	Marked temp. imp. Before treatment, attacks every day and night for 11 mos. For 2 weeks after, occ. attack. Then for 2 wks. recurrence followed by complete freedom with ability to get about for 2 mos. Later recur. with death.
Aortic insufficiency. Dilatation of aorta (*x*-ray). Paroxysmal dyspnea Slight fever. S. P. 118. D. 82.	Noguchi 10/26+++ 11/ 1+++ 11/ 8+++ 11/15+++	11/ 2, 0.3 gm. intraven. 11/13, 0.3 gm. intraven. 11/22, 0.3 gm. intraven.	None None None	1 yr. +. Living	Improvement permanent. Complete disappearance of paroxysmal dyspnea and fever. Well Nov., 1912.

TABLE OF COLLECTED CASES OF SYPHILITIC AORTITIS—(Continued)

No.	Name	Admitted	Sex	Color	Ages	Syphilis	Duration of Illness	Symptoms
11	N	11/ 8/11	M	C	40	20 years	5 years	Pain in chest, acute, radiating to left arm; 1 yr. shortness of breath on slight exertion; edema, cough.
12	N	12/ 1/11	M	W	61	Denies	6 years	Palpitation; slight dyspnea; angina pectoris.
13	T	12/17/11	M	W	47	28 years	9 months	Pain in chest at first. Two violent attacks of dyspnea; palpitation, general weakness, no edema.
14	B	3/ 2/12	M	W	51	25 years	2-3 years	Dyspnea slight on exertion. Angina pectoris for 1 year.
15	T	3/20/12	M	W	36	19 years	1 year	Angina pectoris on exertion or excitement.
16	W	8/ 2/12	M	W	68	Denies	4 months	For 4 mos. attacks of dyspnea, pain over heart radiating to left shoulder; 3 wks., edema. One transient attack of blindness.
17	R	5/ 6/12	F	W	53	?	6 months	Weakness, loss of weight, fever.
18	C	9/ 9/12	F	C	38	+	6 months	Palpitation, shortness of breath, pain over heart, occasionally attacks of dyspnea at night.
19	L	9/11/12	F	W	39	?	9 months	Attacks of angina with dyspnea on exertion; 5 days edema.
20	Mc	8/31/12	M	W	50	9 years	8 months	Dull pain in left shoulder, constant; later down left arm; 4 mos. dyspnea; 1 mo. aphonia.

TABLE OF COLLECTED CASES OF SYPHILITIC AORTITIS—(Continued)

Diagnosis	Wassermann	Salvarsan	Reaction	Entire Duration of Disease	Remarks
Dilatation of aorta (*x*-ray), anginal pain, broken compensation, enlarged heart with mitral insufficiency. S. P. 105. D. 65.	11/15+++ 12/ 8— 1/26— 3/22—	11/24, 0.3 gm. intraven. 12/ 1, 0.3 gm. intraven. 12/ 8, 0.3 gm. intraven. 12/16, 0.3 gm. intraven.	None None None None	6 yrs. +. Living	Complete disappearance of pain. Repeated attacks of broken compensation. Doing fairly well.
Angina pectoris. No dilatation of aorta (*x*-ray). S. P. 150. D. 104.	12/10++	12/29, 0.3 gm. intraven.	Slight	6 yrs.6 mos. +. Living	Greatly improved. Still doing well.
Aortic insufficiency. Aneurysm of arch of aorta (*x*-ray). S. P. 184. D. 70.	12/ 8+++ 12/20++ 1/12— 8/20—	12/ 8, 0.3 gm. intraven. 12/15, 0.3 gm. intraven. In next mo. 2 doses 0.3 gm. intraven.	Slight	1 yr. 6 mos. Living	Improved. No symptoms. Gained strength. Symptomatically well.
Dilatation of arch of aorta (*x*-ray); systolic murmur at base; slight cardiac hypertrophy; tabes dorsalis: angina. S. P. 130. D. 90.	3/28+++ 4/ 3++	3/28, 0.2 gm. intraven. 4/ 5, 0.3 gm. intraven. 4/14, 0.3 gm. intraven.	None None None	3 yrs. + Living	Well up to the present time; working.
Aortic insufficiency. No dilatation of arch (*x*-ray). Angina pectoris.	5/23++ 5/29—? 6/13± 9/11+++	5/23, 0.3 gm. intraven. 5/29, 0.3 gm. intraven. 6/ 6, 0.3 gm. intraven. 6/20, 0.3 gm. intraven. 7/15, 0.6 gm. intraven. 9/13, 0.6 gm. intraven. 9/25, 0.6 gm.	None None None None None Vomiting	1 yr. 5 mos. Dead	Improvement with temporary cessation of attacks after each dose. Herxheimer reaction. Sudden death Oct. 1, 1912
Aortic insufficiency: aortic dilatation (*x*-ray). Paroxysmal dyspnea with pain. S. P. 186. D. 58.	6/23+++	8/24, 0.3 gm. intraven.	Slight	4 mos. Death	Sudden death within 48 hours of salvarsan.
Aortic insufficiency; fever; anemia.	5/11+++ 5/23+++ 5/29+++ 6/12++	5/16, 0.3 gm. intraven. 5/23, 0.3 gm. intraven. 6/ 6, 0.3 gm. intraven.	None None Vomited	11½ mos. Death	Moderate improvement. Loss of fever after injections of Hg. Death Oct. 12, 1912, of cardiac decompensation.
Aortic insufficiency; dilatation of aorta. S. P. 165. D. 60.	9/13+++	9/19, 0.3 gm. intraven.	Fever	6 mos. Living	.....
Aortic insufficiency; dilatation of arch (*x*-ray). Attacks of angina and dyspnea. S. P. 155. D. 50.	9/20+++	9/13, 0.3 gm. intraven. 4/20, 0.3 gm. intraven.	None Slight	9 mos. Living	Improvement. For 4 days before salvarsan 7 attacks. In next week 2 attacks.
Aneurysm of aorta (*x*-ray); differences in pulses; paralysis of left vocal cord; pressure on left bronchus.	9/ 6+++ 9/13++	9/ 7, 0.3 gm. intraven. 9/13, 0.3 gm. intraven. 9/20, 0.3 gm. intraven. 9/28, 0.3 gm. intraven. 10/ 8, 0.3 gm.	None None Slight	8 mos. Living	No improvement.

TREATMENT

Since the recognition of the syphilitic origin of certain cardiovascular diseases, antisyphilitic treatment has been recommended and used with varying degrees of success (Huchard, Fournier, Osler, Allbutt). It is usually stated that such treatment may bring about relief from pain. Within the last few years, however, more particular attention has been paid to the treatment of these cases. Goldscheider thinks that the outlook is poor. Potassium iodid is insufficient and must be combined with mercury or salvarsan. Oigaard, on the other hand, reports rather satisfactory results with the use of mercury and iodid. In this manner he has treated fifteen patients with marked improvement in all cases. This benefit showed itself by the disappearance of substernal pain, angina and paroxysmal dyspnea, in increasing strength and returning ability to work, and an improvement in the anemia when this was present. The relationship which he found to exist between the Wassermann reaction and disappearance of symptoms is interesting. In six cases the Wassermann test became negative during the first cure, which lasted about three months; in the remaining cases the reaction disappeared more slowly, and only after two or three courses of treatment. In three instances there was a return of symptoms while the Wassermann was still negative, while in four the symptoms disappeared before the Wassermann.

With the introduction of salvarsan, Ehrlich's original warning against the use of this drug in the presence of cardiovascular disease prevented for some time its employment in syphilitic aortitis, but now sufficient data have accumulated to show that the danger under such conditions is slight. Breitmann, who collected the cases of death after salvarsan injections, reported in the literature, has discussed this question quite fully from a theoretical standpoint. He thinks the drug may prove dangerous when there is disease of the coronary arteries.

The experimental work of Auer[71] has shown that salvarsan injected intravenously in acid solution is dangerous. Rabbits and dogs injected intravenously with 0.5 per cent. acid solutions develop cardiac dilatation, and show abrupt fall in blood-pressure with immediate death. The intravenous injection of 0.5 per cent. alkaline solution in dogs seems to have little effect on the blood-pressure, and no marked effect on the heart, though its factor of safety may be so reduced in some instances that an extra strain brings on fibrillation and death. With higher dilutions of the drug, even acid solutions may be harmless when injected slowly. The alkaline solution employed by Auer is five times as strong as that used for man in whom 0.1 per cent. solutions are employed. Hoke and Rihl,[72]

71. Auer: THE ARCHIVES INT. MED., 1911, viii, 169; Jour. Exper. Med., 1911, xiv, 248.

72. Hoke and Rihl: Ztschr. f. exper. Path. u. Therap., 1911, ix, 332.

who experimented with intravenous injections of 0.5 per cent. salvarsan in alkaline solution state that such a solution will lower the blood-pressure in rabbits, but that this is principally due to its effect on the central nervous system, and not on the heart and blood-vessels directly.

From a practical standpoint the use of salvarsan in syphilitic aortitis seems to be comparatively harmless, though later I will point out a possible source of danger when large doses are given; and the main point at issue is as to whether it is of real benefit. Weintraud[56] has reported the results of treatment by salvarsan of twenty-six cases of syphilitic heart and arterial disease. The cases included aortic insufficiency, angina pectoris, myocardial disease with syphilitic arteritis and sclerosis of the cerebral arteries. He has not seen any ill effects from the injections. Two to four injections of 0.2 to 0.5 gram were given. In many of the cases there were no symptoms, or where symptoms were present they were so mild that any benefit derived from the injections could not be estimated. In only three cases, all of aortic insufficiency with angina, could he be sure of improvement. Others, too, have used salvarsan in isolated instances, but give little information as to its value (Fiessinger, Goldscheider, Biermann, Hirtz and Braun, Schminke[73]).

Salvarsan has been given to 20 of my series of cases. Among these there were 14 of aortic insufficiency, 9 of which were associated with angina pectoris, or attacks of paroxysmal dyspnea, one of these latter having an aneurysm as well, 5 cases of aortitis associated with true angina, anginal pain or cardiac enlargement, and 1 case of aneurysm.

The drug has been given for the most part intravenously, but in 6 cases it was used before the intravenous method of administration became general, and was then given by the Lesser method intramuscularly. Three of these patients received intramuscular injections of 0.6 gram, 2 received 0.45 gram, and 1, 0.5 gram. The remaining 14 cases have usually been given several doses of 0.3 gram intravenously. In this manner of divided dosage 4 cases have received 0.3 gram each, 2 cases 0.6 gram each, 4 cases 0.9 gram each, 1 case 1.2 gram, 1 case 1.8 gram and 1 case 3.0 grams. The doses have been given usually at intervals of eight to ten days. Salvarsan reactions have not been very common. Severe reactions with chills, fever and vomiting or diarrhea have occurred only six times in the thirty-seven administrations. During the last year freshly distilled water has always been employed.

In choosing the dosage I preferred to administer small amounts repeatedly, rather than one or two full doses; and after my rather limited experience this attitude seems justifiable, for it is possible that there is some danger in giving large doses, particularly in patients with angina pectoris and paroxysmal dyspnea.

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73. Schminke: Reichs. Med. Anz., Leipz, 1911, xxxvi, 513, 545.

Although death has occurred in eight of the twenty cases, in only one instance could it be even remotely connected with the injection. This one patient suffering from aortic insufficiency, and severe attacks of paroxysmal dyspnea and anginal pain, died suddenly within forty-eight hours of the first intravenous injection of 0.3 gram. Even this may have been a coincidence, for on another occasion a patient with angina died suddenly on the day before the first injection was to be made. Cardiac decompensation alone certainly does not seem to be a contra-indication. Seven patients were in a critical condition from decompensation when the first dose was given. Except in the case just described, if any effect was produced it was improvement.

All of the fatal cases suffered from aortic insufficiency. Four patients died of cardiac failure, one three weeks, three six months after treatment; one patient died of angina pectoris seven months after treatment; while one patient committed suicide one month after treatment.

In only one case (No. 6) was it possible to obtain an autopsy. The patient was in a hopeless state of cardiac decompensation when 0.45 gram of salvarsan was injected intramuscularly. He died three weeks later. Autopsy showed the typical gross appearance of syphilitic aortitis. Microscopically the lesion in the aorta appeared perhaps somewhat less cellular than the average, but did not differ materially from the lesions which have been seen in a number of other cases.

SUMMARY

The twenty treated cases have been summarized in the accompanying table (Table 1). It may be said once and for all that I have observed no definite beneficial effect on the cardiac incompetency itself, nor has there been any change in the anatomical condition. Signs of aortic insufficiency have not been reduced, nor have aneurysms grown smaller. And, indeed, when one comes to draw conclusions relative to the effect of certain therapy in a group of cases, the symptoms of which are so manifold and so varying, I am aware that the most extreme precautions are necessary. In such a small group, too, coincidences may deceive one, and I have therefore attempted to preserve as critical an attitude as possible.

It has, however, been impossible to escape from the fact that certain of these patients have been benefited by salvarsan treatment, and this after all is not especially surprising, for these individuals must be regarded as suffering not only from a mechanical defect in the circulatory apparatus, but as well from a localized chronic infection. Thus it is reasonable to suppose that if this infective process is ameliorated, or cured, the general condition of the patient will likewise improve. In most instances this has been the case. The majority of patients feel considerably better after one or two injections. The patients who have

improved sufficiently to go back to work report that they feel stronger and better than they have for years. Few, however, have gained weight, though the appetite increases.

The most striking result, however, has been the effect of treatment on the pain and attacks of paroxysmal dyspnea. In all but four cases, there has been permanent, or marked temporary or immediate improvement in this condition. In five cases there has been up to the present time permanent relief of pain. Two of these patients (Nos. 4 and 5) had suffered for one year when first observed. At the present time, two years after treatment, they are well and working hard. One patient (No. 14), who had suffered constantly from angina pectoris for two or three years, is well and working seven months after treatment. The fourth patient (No. 13), with aortic insufficiency, aneurysm and occasional attacks of paroxysmal dyspnea, is well and working hard six months after treatment; and in the fifth case (No. 11), though there has been repeated decompensation, pain of anginal nature which had existed for five years, has recurred but once over a period of ten months.

In six cases there has been most striking temporary improvement. Two cases (Nos. 7 and 9) that had suffered for about a year with paroxysmal dyspnea accompanied by excruciating anginal pain, obtained complete temporary relief. This lasted in one instance for two months during which time the patient was able to go about and do a little work. At the end of this time the attacks recurred, became progressively worse and the patient finally died. In the other case the improvement of much the same nature, lasted only about four weeks. In another case (No. 2) there was relief from pain for six months. At the end of this time the pain recurred, and since then the patient has had almost constant decompensation. In one most striking case of angina pectoris (15) lasting over a period of one year, with sometimes six and eight attacks a day, there has been almost, or indeed entire relief for periods of three weeks to a month after the injections of salvarsan, during which time the patient could attend to his daily work. At the end of this time the attacks recurred, gradually becoming more frequent and more severe, until he finally returned to the hospital for treatment. Occasionally he only remained in the ward one or two days, and twice only one night, so that the effect of rest or diet can be excluded. A second patient with angina pectoris (No. 12) left the hospital much improved and remained well for four weeks. Later he was lost sight of. Finally, a woman who had attacks of angina for nine months almost daily, and on any slight exertion, improved immediately while in the hospital, but later had a recurrence. During four days before salvarsan was given there were seven attacks. During the next two weeks after two doses of 0.3 gram of salvarsan, there were but two attacks.

In the remaining cases there was one patient with aortic insufficiency with severe broken compensation (6), who was apparently unaffected; one of severe angina pectoris and aortic insufficiency (No. 8), who, after one intramuscular injection, showed no definite improvement, and died during an attack. One patient (No. 16), already described, who died forty-eight hours after the first injection; while the pain in one case of aneurysm with cervicobrachial neuralgia was uninfluenced after four intravenous injections of 0.3 gram. The remaining five cases improved considerably during their stay in the hospital, but have either been under observation too short a time to say what the result will be, or have been lost sight of.

In the study of these cases one fact has been very strongly impressed on me, and that is the persistence of a positive Wassermann reaction, or the rapid return of a positive reaction after a temporary abatement during treatment. There were eleven cases in which the Wassermann test could be repeatedly performed. In four of these only has it been possible to obtain, so far, a persistently negative reaction. All four cases showed marked improvement in symptoms (Nos. 2, 5, 11 and 13). In the cases (Nos. 9 and 15) it has diminished in intensity coincident with a relief in symptoms only to return again and become strongly positive with the recrudescence in one instance of attacks of paroxysmal dyspnea, and in the other of angina pectoris. In the latter case the reaction was still positive, even though 3 grams have been given. In five other cases it has remained positive after the injection of 0.9 gram intravenously, and in one case after the injection of 0.6 gram intravenously. But the first relief of symptoms, even though temporary, has come soon after the first or second injection in most instances, and while the Wassermann reaction was still positive.

Thus the improvement in symptoms manifests itself very rapidly, and usually within four to six days after the injection. We have, however, noticed an interesting phenomenon in a number of instances, namely, an increase in severity of symptoms within twenty-four to forty-eight hours after intravenous injections. This has been most striking in cases of angina pectoris and paroxysmal dyspnea. During the day or two following injections the paroxysms of dyspnea or attacks of angina increase in severity and number, then rapidly diminish and entirely disappear. This was most striking in one case of angina pectoris that received on three occasions 0.6 gram intravenously. A careful record was kept of the number of attacks during these periods and the accompanying chart (Fig. 6) illustrates the characteristic effect.

I cannot but feel convinced that treatment by salvarsan does have a distinctly beneficial effect on the pain and paroxysmal dyspnea in syphilitic aortitis, but as I have had more and more opportunity to study these cases, it has become increasingly evident that a cure is exceedingly

difficult to accomplish. But the very rapid amelioration of the pains, attacks of angina pectoris and paroxysmal dyspnea is not only important for the patient, but perhaps suggests certain explanations for these symptoms. So closely are the attacks of paroxysmal dyspnea associated with angina pectoris in this group of cases that here at least I prefer to consider them together.

I am aware that many explanations have been offered to account for the phenomena, and the theories of angina pectoris are legion. The frequent occurrence of lesions about the sigmoid region, and in the immediate vicinity of the coronary arteries, has led most observers to

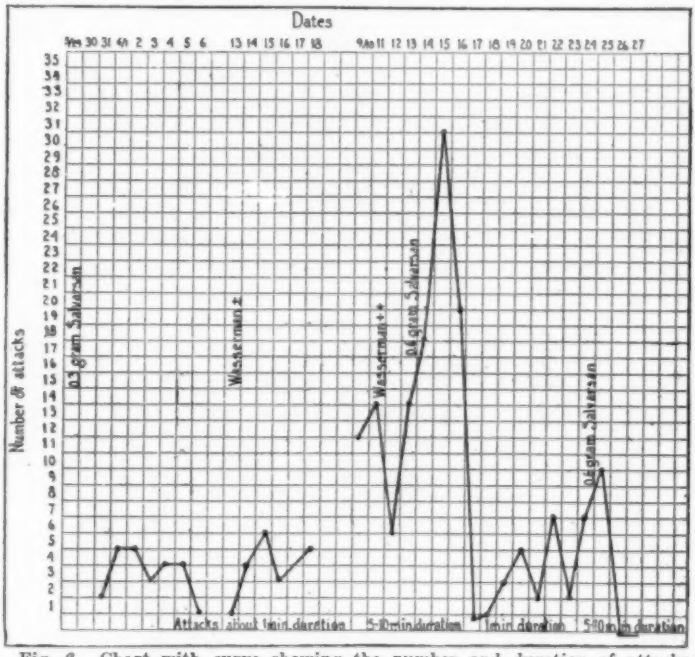

Fig. 6.—Chart with curve showing the number and duration of attacks of angina following the intravenous administration of salvarsan in a case of angina pectoris.

infer that disturbances in coronary circulation in this class of cases was responsible for the attacks of angina pectoris, and, perhaps, the attacks of paroxysmal dyspnea as well. The conditions, however, are complicated. One has to deal with an active infection at the root of the aorta to which the nerve supply is rich, and where in consequence disturbing reflexes may be excited; frequently involvement of the coronary circulation, and in a large proportion of instances, actual insufficiency of the aortic valves with the resultant changes in pressure in the left ventricle and their effects. It is impossible here to discuss the subject of angina

pectoris. I need only refer to the works of Huchard, Rosenbach,[74] Osler,[75] Von Neusser[76] and Mackenzie.[77]

We have not in the least been able to convince ourselves from autopsies in these cases that there was any direct association between disease of the coronary arteries and attacks of angina pectoris or paroxysmal dyspnea. Almost complete occlusion of the mouths of the coronary arteries has been found without either symptom appearing during life, and attacks of angina and paroxysmal dyspnea have occurred in cases which at autopsy showed large coronary arteries with wide mouths.

That these attacks may be associated with acute distention of the ventricle is possible, since all have occurred in cases of aortic insufficiency, but certainly such attacks are much more common in syphilitic aortitis than in aortic insufficiency caused by rheumatic fever.

The study of my cases, however, has suggested very strongly that these symptoms are closely associated with the inflammatory reaction at the root of the aorta, and are directly dependent on it. The fact first that symptoms may increase temporarily in severity following intravenous injections of salvarsan, and that the most pronounced reactions have occurred with the largest doses lends support to the idea that this represents, as it were, a Herxheimer reaction, and that the increase in symptoms is due to the increased reaction of the tissues towards the liberation of toxin in excess from rapidly destroyed spirochetes. Following this there is rapid subsidence of symptoms, so rapid, indeed, that it could scarcely be ascribed to very great modification in anatomical structure. There might, however, be rapid improvement in the inflammatory reaction. Finally, the temporary relief of symptoms with severe recrudescences could best be explained by associating the symptoms directly with the progress of the inflammation.

The paroxysmal dyspnea, as I have already suggested, simulates very closely an attack of asthma, and on account of the sudden onset, the violent type of expiratory dyspnea with suffocating sensations, the acute emphysema, and rapid subsidence, it impresses one as an acute temporary bronchospasm. That such an explanation holds for many cases of true asthma, seems most probable. Indirectly, too, the recent experiments of Januske and Pollak[78] have some bearing on the question, for they have been able to offer an explanation for the beneficial effect of epinephrin in asthma. They found that the marked bronchiospasm caused by the injections of muscarin or peptone in animals was promptly relieved by injections of epinephrin and less rapidly, but more permanently by atropin. Pal,[79] too, has reported that such substances as epi-

74. Rosenbach: Die Krankheiten des Herzens, 1897.
75. Osler: Angina Pectoris, 1897.
76. Von Neusser: Angina Pectoris, 1909.
77. Mackenzie: Lancet, London, 1895, i, 16.
78. Januske and Pollak: Arch. f. exper. Pathol. u. Pharmakol., 1911, lxvi, 205.
79. Pal: Deutsch. med. Wchnschr., 1912, xxxviii, 5.

nephrin, atropin, caffein and the nitrites which act as vasodilators to the coronary arteries, produce a dilatory effect as well on the bronchial musculature. Recently Park,[80] by direct experiment, has confirmed these results obtained with epinephrin. In the cases of paroxysmal dyspnea nitroglycerin, as mentioned before, seems to have some effect in cutting short the attack, and in cases which have been watched for days or even weeks in the wards before salvarsan was given it was the only drug which seemed to have any influence. It is possible that, if it had any effect at all, it is through a relief of bronchiospasm, and not from its action on the coronary arteries. Atropin has been employed a few times, but not sufficiently often to say anything regarding its action. Epinephrin I have feared to use.

Having still more important bearing on this subject are some old experiments of François Frank[81] on aortic reflexes. By irritating the inner surface of the aorta of dogs he was able to produce quite constantly certain respiratory phenomena. These consisted of three types: (1) Sudden apnea with the respiratory muscles in spasm either during the inspiratory or expiratory phase, or apnea with general inhibition of all respiratory movements; (2) tachypnea, without severe constitutional symptoms, and (3) a slow dyspnea of severe and grave form. The cause of this dyspnea he showed quite plainly was spasm of the bronchial musculature. He believed, too, that there was coincident contraction of the pulmonary artery. Associated with this type of dyspnea was a contraction of the peripheral vessels and rise of blood-pressure. Occasionally a spasm of the laryngeal muscles occurred. In other cases he was able to produce all the signs of aortic insufficiency (the capillary and collapsing pulse) save a diastolic murmur through irritation of the root of the aorta and without injury to the sigmoid valves. Stewart[82] has observed this last phenomenon and considers it as a reflex from the root of the aorta, and in some experiments in which aortic insufficiency was performed on dogs I have repeatedly confirmed this observation. That Frank's respiratory phenomena have not been noted since is almost certainly due to the method of experimentation, for in Stewart's experiment, and in those which others have performed, full ether anesthesia or artificial respiration was employed.

It is thus evident that disturbing reflexes may be set up experimentally in animals by irritation of the root of the aorta, and there is no reason to suppose that the same thing should not be true for man. The dyspnea caused by bronchiospasm, and the contraction of the peripheral arteries producing heightened blood-pressure in the experimental animal

80. Park: Jour. exper. Med., 1912, xvi, 568.

81. Frank, François: Arch. de Physiol., 1890, series 5, ii, 508 and 547; Jour. de l'anat., 1877, xiii, 545.

82. Stewart: The Archives Int. Med., 1908, i, 102.

is a close reproduction of the paroxysmal dyspnea as it occurs in syphilitic aortitis, and it seems quite justifiable to suggest that the two conditions are the same. It would be difficult to explain the increase in blood-pressure which occurs during these attacks in man on the presence of pain, or of cyanosis, for pain is frequently absent and dyspnea may continue for some time (fifteen to thirty minutes) after the sudden drop in blood-pressure which comes with the relief of acute symptoms. Our observations, therefore, seem to lend strong support to the idea that these symptoms are dependent on a reflex generated at the root of the aorta by the syphilitic inflammatory process.

Hoover[83] has recently called attention to certain respiratory phenomena which he believes are associated with disturbances of the vagus nerve. In two cases there were attacks of paroxysmal dyspnea and acute emphysema associated in one with an inflammatory mass in the mediastinum, and in another with aneurysm of the arch of the aorta. In both these cases the vagi were found at autopsy involved in the tumor masses. In two other cases of aortic insufficiency there occurred attacks of tachypnea associated with slow pulse. Both patients were relieved by atropin.

Though there is no positive evidence other than the results of treatment that the cases of angina pectoris as well as those of paroxysmal dyspnea in this group are of reflex origin, the definite Herxheimer reaction combined with the rapid improvement and later recurrences suggest that the actual inflammation of the wall of the aorta is of great importance in determining the onset of these attacks. The immediate cause of the attacks of angina may of course be constriction of the coronary arteries, but the true etiology probably lies in the diseased aorta, and not in the coronary arteries themselves.

There are not lacking those who have regarded angina pectoris as a reflex depending on reflex nerve impulses. Nothnagel's[84] theory of angina pectoris vasomotoria is well-known. Huchard, though recognizing that inflammations about the root of the aorta might cause a reflex angina pectoris from involvement of the nerves, would exclude such cases from the category of true angina pectoris. Recently this whole question has been discussed by Heitz.[85] Actual disease of the cardiac plexuses has been described by Benenati[85] in two of three cases of syphilitic aortitis with angina pectoris, but others have not been able to confirm these findings. It does not seem necessary, however, to presuppose such lesions, since involvement of the nerve endings in the root of the aorta might be sufficient to determine the onset of reflexes.

The question, of course, complicated as it is, should be put to experimental proof before going further, but the suggestion that these attacks

83. Hoover: Jour. Am. Med. Assn., 1911, lvii, 1733.
84. Nothnagel: Deutsch. Arch. f. klin. Med., 1867, iii, 309.
85. Benenati: Riforma med., 1902, ii, 326.

of paroxysmal dyspnea and angina pectoris in this particular class of case are directly connected with the syphilitic inflammation at the root of the aorta, and that these symptoms are of reflex nature rather than dependent on anatomical lesions of the coronary arteries, seems in accord with my observations.

The permanent relief of these symptoms can only be obtained, if at all, by the most persistent treatment. It is probably difficult to reach the spirochetes by the blood-stream, so that the diseased aorta is hard to attack. I have been more and more impressed with the necessity of giving repeated doses of salvarsan, and am now not as much discouraged by recurrences as at first. It may be that neosalvarsan will prove more efficacious, or the combination of salvarsan with injections of mercury. Salvarsan, however, would seem to be the best method of primary attack, since the symptoms which may be relieved are immediately dangerous to the life of the patient. The possibility of producing a Herxheimer reaction in cases with paroxysmal dyspnea and angina pectoris should be constantly borne in mind, and in such instances full doses might bring about an alarming immediate increase in symptoms or sudden death.

CONCLUSIONS

Syphilis produces a characteristic lesion of the aorta, which is responsible, as is shown by autopsy statistics and the Wassermann reaction, for most aneurysms, about 75 per cent. of cases of aortic insufficiency in adults, many cases of dilatation of the aorta, and a certain group of cases of angina pectoris.

The infection of the aorta probably takes place during the secondary stage, and though the symptoms and signs of syphilitic aortitis with the complications may develop within a few months of infection, the process usually remains latent, or unrecognized for an average of sixteen to seventeen years. Thus, syphilitic aortitis is probably a common cause for the presence of a positive Wassermann reaction in so-called latent syphilis.

The early symptoms and signs of syphilitic aortitis are a positive Wassermann reaction, precordial pain, slight dyspnea, attacks of paroxysmal dyspnea and angina pectoris, cardiac hypertrophy, increased pulsation of the vessels of the neck and signs of dilatation of the aorta.

The precordial pain, paroxysmal dyspnea and angina pectoris are temporarily or permanently relieved by repeated injections of salvarsan, but in certain instances these symptoms, especially after large doses, may be aggravated for the first forty-eight hours after injection.

The paroxysmal dyspnea, which may be regarded as acute bronchiospasm, and possibly the angina pectoris in syphilitic aortitis is dependent on the inflammatory reaction in the wall of the aorta, and may be regarded as reflex disturbances set up by the syphilitic process involving the root of the aorta.

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THE MINUTE VOLUME AND ALVEOLAR AIR IN PULMONARY EMPHYSEMA *

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This discussion will deal with two phases of pulmonary emphysema which have to do with the lung as a respiratory organ quite apart from the respiratory threshold, minute-volume of blood passing through the pulmonary circulation and influences from the peripheral nerve supply of the respiratory organs.

Patients who apparently have the same degree of emphysema behave in different ways. One of my patients had pronounced cyanosis, a respiratory rate of 16 to 18 per minute, a minute-volume of respired air of 8 liters. Co_2 content of his alveolar air was 8.55 per cent. This patient did not suffer from air hunger and never had an asthmatic attack.

The second patient presented two phases. On admission to the hospital he was cyanotic. The respiratory rate was 14 per minute. The minute-volume of respired air was from 8 to 10 liters. The alveolar air contained 7.2 per cent. of Co_2 and air hunger was pronounced. A few days later conditions improved. He no longer suffered from air hunger, but the respiratory rate was 15 per minute, the minute volume of respired air was 6.380 liters. His alveolar air contained 5.3 per cent. of Co_2 and cyanosis had disappeared. At first glance one would say the lung ventilation was much better during the first period and therefore the real difficulty consisted in an impairment of the lung as the organ of external respiration; i. e., the lung did not afford a good medium for the interchange of carbon dioxid and oxygen between the blood and alveolar air. But we will see later in the discussion the real difficulty did not consist in an impairment of the respiratory function, but in the ventilation function. Thus far my observations have been made on cases of marked emphysema which differed much in the clinical symptoms of cyanosis, air hunger and minute-volume of respired air. But when this external respiration was investigated it was found that the patients all suffered from impaired ventilation, but reacted differently. A significant clinical test carried out on the patients substantiates this explanation. None of

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these patients showed the slightest modification of their symptoms when they breathed an atmosphere of pure oxygen. In other words they were not suffering from a low oxygen content, but from a high carbon dioxid content of their alveolar air and this can be ascribed only to impaired ventilation.

Patients who suffer from an impairment of the external respiratory function must of necessity get relief from the inhalation of oxygen. This is very clearly demonstrated in pulmonary edema and bronchopneumonia of children, whose cyanosis is instantly relieved by the inhalation of oxygen, when the real difficulty is impaired ventilation throughout the entire lung. In my personal experience I have known only one patient who got relief from the inhalation of oxygen, and I did not have the opportunity of confirming that. I have only the patient's personal testimony and that must be received with caution from emphysematous and asthmatic persons.

The significance of pathological changes in the alveolar walls of atrophic emphysematous lungs seems very doubtful in all of the cases I have studied. Inhalation of oxygen is a good clinical method of differentiating between these two functions, viz., external respiration and lung ventilation.

The early observations on the first patient were made with the aid and direction of Dr. J. J. R. Macleod in the physiological laboratory. I wish here to express my thanks and acknowledge the debt of gratitude I owe him for his active aid and instruction in the use of the physiologist's methods of studying respiration and for many helpful suggestions.

The method used in studying alveolar air is that described by Haldane and Priestly.[1] Specimens of the tidal air were procured by Zuntz's method, and the analyses of the respired air were made with Haldane's modification of Petterson's[2] apparatus.

The first patient was a man 46 years old, 5 ft. 6 in. high, and weighing 140 pounds when these observations were begun in December, 1910.

The patient had pronounced cyanosis of the lips, nose, ears, tongue and fingers. Drumstick finger tips were marked. The patient denied ever having had any attack of asthma or experiencing the sense of air hunger. His persistent complaint was a sense of fulness and slight pain over the frontal region and a sense of fulness and pressure in the epigastrium. There was moderate cough and very little expectoration. At this time in 1910 the patient worked as presser in a garment factory and suffered no inconvenience at his work on account of the emphysema.

The heart's apex was in the sixth interspace and the left border of the heart extended 14 cm. to the left of the median line in the sixth interspace. The right cardiac border extended 6 cm. to the right of the median line in the fourth interspace. There were no murmurs nor accentuation, nor palpable thrills or palpable closures from any of the heart's valves. The veins of the neck and upper extremities were rather large but no abnormal venous pulsations were visible. There

1. Jour. Physics, xxxii, 227.
2. Petterson: Ztschr. f. Analyt. Chem., xxv, 467.

were no signs of any impairment of the mass movement of blood and Dr. G. N. Stewart[3] estimated the mass movement through the hands, and found it quite normal according to his method.

The lungs were very emphysematous. The lower borders were at the ninth rib in the axillary line on both sides and filled the pleural sinus posteriorly.

The costal angle was not enlarged during inspiration and the antero-lateral portion of the thoracic wall from the sixth to the ninth ribs, inclusive, were drawn toward the median line during inspiration. The epigastrium was protruded but the lower end of the sternum was drawn toward the vertebra. From a posterior view one sees, however, a distinct increase in the transverse diameter of the base of the thorax in the plane of the posterior axillary line. When the diaphragm occupies a low position the following phenomena are observed during respiration: Retraction of the lower end of the sternum, a narrowing or a want of enlargement of the costal angle and approximation of the hypochondria and protrusion of the epigastrium. These signs were always very pronounced in this patient for the two years he was under observation. Auscultation revealed the characteristic prolonged expiratory murmur and an abundance of coarse and medium dry and an occasional moist râles during inspiration and expiration.

The patient had a moderate cardiac enlargement without any signs of disease of either the pulmonary or aortic arterial systems. No signs of mediastinal disease or disease of the pericardium. The minute-volume of blood was normal.

The striking feature about this patient was the cyanosis without dyspnea and without any indication of cardiovascular disease.

The alveolar air was estimated a great many times over a period of sixteen months and the CO_2 content was never lower than 7.5 per cent. and was most of the time between 8.1 per cent. and 8.5 per cent.

October 14, 1911, the following four analyses were made of the alveolar air:

1. CO_2 = 8.35 per cent.
   O_2 = 11.70 per cent.
2. CO_2 = 8.99 per cent.
   O_2 = 12.70 per cent.
3. CO_2 = 8.2 per cent.
   O_2 = 12.41 per cent.
4. CO_2 = 8.55 per cent.
   O_2 = 11.04 per cent.

The cyanosis and partial pressure of CO_2 in the alveolar air sustained a very constant relation to each other. January 20, 1911, when he was able to be at work and had pronounced cyanosis the alveolar air contained in two analyses 7.3 per cent. and 7.5 per cent. of CO_2. December 11, when he was admitted to the hospital complaining of headache and a sense of pressure in the epigastrium and had too a marked increase of the bronchial symptoms and intense cyanosis, the *alveolar air* contained 9.7 per cent. of CO_2 and 10.73 per cent. of oxygen.

On the former occasion when the CO_2 content of the alveolar air was 7.5 per cent. the respiratory rate was 18 per minute and the minute-volume was 8.530 liters.

On the latter occasion when cyanosis was much more intense, the respiratory rate was 19 per minute, the CO_2 content of the alveolar air was 9.7 per cent. and the minute-volume was 8.530 liters. He not only tolerated a high CO_2 content of the alveolar air at all times but tolerated an increase from 7.5 per cent. to 9.7 per cent. without air hunger or any material change in the rate or minute-volume of respiration. This is a striking result when compared with the intolerance of CO_2 in normal persons, and also when compared with the tolerance of an increase in the CO_2 of the patient's alveolar air, after forced breathing and attempts at holding the breath to the breaking point.

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3. Stewart, G. N.: Heart, iii, 33 and 76.

March 17, 1911, the following experiments were made:

The alveolar air of Drs. Macleod, Wycoff and myself contained the following:

J. J. R. M.	= 5.67 per cent. CO_2	C. F. H.	= 5.1 per cent. CO_2
C. W.	= 5.8 per cent. CO_2	Patient Sam B.	= 8.1 per cent. CO_2

We then took the alveolar air of each at the breaking point after holding the breath as long as possible with the following results:

J. J. R. M.	= 6.71 per cent. CO_2	C. F. H.	= 6.71 per cent. CO_2
C. W.	= 7.27 per cent. CO_2	Sam B.	= 9.0 and 9.7 per cent. CO_2

Sam B. then breathed as deeply and as rapidly as possible twenty times in 30 seconds; a period of apnea for 18 seconds followed. Then with the resumption of automatic respiration the alveolar air contained 9.4 per cent. of CO_2. Another time Sam B. breathed twenty-five times in 30 seconds. Apnea for 18 seconds followed, and with the resumption of automatic respiration the alveolar air contained 10.28 per cent. of CO_2. Nine months later when his cyanosis was very intense he did not suffer from air hunger (19 respirations per minute), and the percentage of CO_2 in the alveolar air had attained a percentage which equalled his maximum endurance on the former occasions when the CO_2 in his alveolar air was 8.1 per cent. during tranquil breathing.

There was another point of interest in Sam B. relative to his high respiratory threshold. He never had apnea when awake, but when the inhibition of sleep was added to his ordinarily high respiratory threshold, apnea ensued. In this instance, as in instances of slumber apnea associated with sclerosis of the cerebral arteries, the apnea occurred in light sleep. Jan. 27, 1911, Dr. Macleod took a tracing of Sam B.'s respiration in the pneumograph constructed after Haldane's design. The accompanying tracing shows periods of apnea (Fig. 1). In the tracing the upward stroke marks the expiratory excursion. In watching the tracing we were at first much concerned to see the cessation of respiration, but as the apnea recurred it was observed respiration ceased as the patient's eyelids closed in sleep. We had repeated opportunities to observe this fact. It was interesting to see the upstroke of the lever to the abscissa mark the expiratory phase of the thorax as the eyelids fell in sleep. Unlike the slumber apnea of arterial disease the apnea was not followed by hyperpnea and air hunger. As the apnea ceased and the patient simultaneously wakened and resumed automatic respiration the rate and rhythm and depth of the respiratory excursions were resumed as they were up to the moment of apnea.

On the day the tracing in the pneumograph was taken Sam B.'s alveolar air contained 7.5 per cent., 7.9 per cent. and 8.0 per cent. of CO_2 in three analyses. His minute-volume of respired air was 7.9 liters.

Dec. 15, 1911, Sam B.'s alveolar air contained 9.59 per cent. CO_2 and 10.09 per cent. of oxygen. Cyanosis was much more pronounced than on

the day the pneumograph tracing was made. When his cyanosis was so pronounced and his alveolar air contained 9.59 per cent. CO_2 he would lie in bed and go to sleep for short intervals of five or ten minutes. It was common for him to go to sleep five or six times in an hour, but when he went to sleep he did not cease breathing. It seems the partial pressure

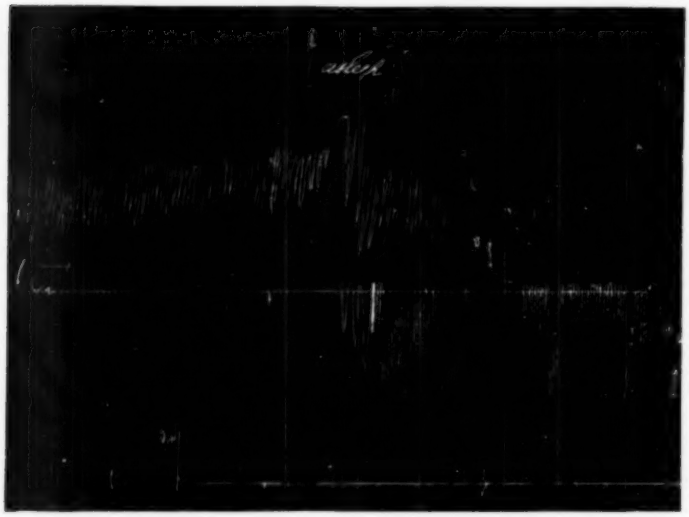

Fig. 1.—Read from left to right. The upstroke marks the expiratory excursion. The arrests of respiration in the expiratory phase mark the points at which the patient went to sleep.

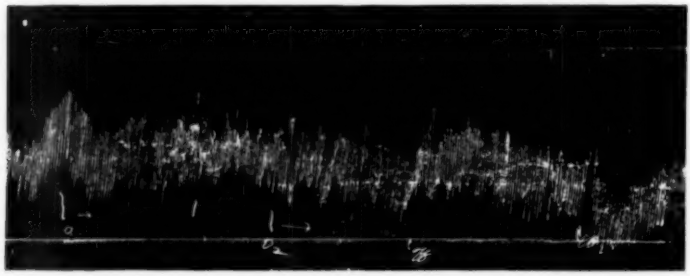

Fig. 2.—Read from left to right. The upstroke marks the expiratory excursion. Note that oxygen in solution did not modify the respiration, whereas the excursions increased the instant some carbon dioxid was introduced into the respired air.

of CO_2 was so high that apnea was never allowed in his moments of slumber. During this period his respiratory rate was 27 per minute, but the minute-volume was only 6.566 liters. When asked if he suffered from

a sense of air hunger he always protested that he had no difficulty in breathing and said his only trouble was headache and a sense of pressure in the epigastrium. The man was really suffering from carbon dioxid poisoning. During the winter and spring we repeatedly gave him large amounts of oxygen to breathe, and although the partial pressure of oxygen in the air he breathed was as high as 50 per cent., it never modified the respiration in any way.

We have in this patient a heightened respiratory threshold with an alveolar air rich in CO_2 and poor in oxygen, without hyperpnea and with a normal minute-volume of respired air. The lung ventilation is therefore apparently but not really good.

The tidal air was then estimated according to Zuntz's method and the alveolar air was analyzed at the same time. It is clear that the CO_2 given off must come from the alveolar air and, as Haldane suggests, if we know the minute-volume of respired air and its content of CO_2 and also the content of CO_2 in the alveolar air, then we have a formula for estimating the proportion of alveolar to tidal air. I have a minute-volume of 8.16 liters. This minute-volume of air contains 3.28 per cent. of CO_2 and my alveolar air contains 5.05 per cent. of CO_2. We have the formula:

$$\text{therefore}\ \frac{\text{3.28 times 8.16 liters}}{\text{5.05}} = \text{alveolar air}$$

Dec. 8, 1911, the Zuntz apparatus was used for collecting a sample of air from Sam B.

Time of collection=10.25 min.
Rate of respiration=12 per min.
Minute-volume=9.16 liters.
Zuntz specimen: CO_2=4.23 per cent. or 0.387 L per min.; O_2=17.45 per cent.
Alveolar air: CO_2=8.3 per cent.; O_2=10.9 per cent.
The alveolar air=4.66 liters which is 50.9 per cent. of the minute-volume. The respiratory quotient=1.2.

Dec. 11, 1911, Sam B. was more cyanotic than at the time the previous specimen was taken. His diet was also more liberal.

Time of collection=11 minutes.
Rate of respiration=19.1 per min.
Minute-volume=8.53 liters.
Zuntz specimen: CO_2=3.84 per cent. or 0.327 L. per minute; O_2=15.94 per cent.
Alveolar air: CO_2=9.77 per cent.; O_2=10.73 per cent.
Alveolar air=3.35 liters or 39.2 per cent. of the minute-volume.
Respiratory quotient=0.7.

Another Zuntz specimen taken the same day.

Time of collection=10 minutes.
Average rate of respiration=27 per min.
Minute-volume=8.73 liters.
CO_2=3.94 per cent. or 0.343 liters per min.
O_2=16.9 per cent. or 0.375 liters absorbed per min.

Alveolar air=3.52 liters or 40.3 per cent. of minute-volume.
Resp. quotient=0.9.
Dec. 15, 1911. Cyanosis very pronounced.
Time of collection=12 min .
Minute-volume=6.566 liters.
Rate of respiration=27 per min.
Zuntz specimen: CO_2=5.21 per cent. per min. = 0.342 liters; O_2=13.495 per cent. or absorbed per min.=0.541 L.
Alveolar air: CO_2=9.59 per cent.; O_2=10.09 per cent.
The alveolar air=3.567 liters or 54 per cent. of minute-volume.
Resp. quotient=0.64.

Compare the results with the same apparatus in my own respiration and we find that my alveolar air varied from 64 to 82 per cent. of the minute-volume. When my respiratory rate was 10 per minute the alveolar air constituted from 64 to 77 per cent. of the tidal air. Whereas, Sam B.'s alveolar air constituted only 50.9 per cent. of the tidal air when he was breathing twelve times per minute and had a minute-volume of 9.16 liters.

It is obvious that if the minute-volume remains the same a slower rate of respiration will give a larger percentage of alveolar air in the minute-volume than when the rate of respiration is increased.

On Dec. 15, 1911, a Zuntz specimen was taken from me with the following results:

Time of collection=12 min.
Rate per minute=10.
Minute-volume=8.16 liters.
This specimen contained: CO_2=3.28 per cent.; O_2=17.27 per cent.
The alveolar air taken at the same time contained: CO_2=5.05 per cent.; O_2=14.9 per cent.
Respiratory quotient=0.85.
The alveolar air, therefore, equalled 64.8 per cent. of the tidal air.
From C. F. H.—Another specimen Dec. 19, 1911.
Time of collection=11 min.
Rate of resp. per min.=10.
Minute-volume=8.081 liters.
This specimen contained: CO_2=3.78 per cent.; O_2=16.225.
The alveolar air contained: CO_2=4.86 per cent.; O_2=15.24 per cent.
Respiratory quotient=0.75.
The alveolar air constituted 77.7 per cent. of the minute-volume.

At a later date the experiment was tried of breathing as nearly fifteen times per minute as I could. The alveolar air at this time, in July, 1912, a warm day, contained 4.5 per cent. CO_2.

The following are the results from three Zuntz specimens C. F. H.:

1. Time of collection=12 min.; minute-volume=8.13 L.; R. rate=15.1 per minute; CO_2=2.7 per cent.; Alveolar air=60 per cent.; CO_2 per minute, 222 c.c.

2. Time of collection=8 min.; Minute-volume=9.14 L.; R. rate=16 per min.; CO_2=2.7 per cent.; Alveolar air=59.9 per cent.; CO_2 per minute = 246 c.c.

3. Time of collection=7 min.; Minute-volume=9.76 L.; R. rate=16.3 per min.; CO_2=2.4 per cent.; Alveolar air=53.3 per cent.; CO_2 per min.=234 c.c.

From these results it seems quite clear that the dead space in emphysema must be increased. There must be a considerable expansion of the lung between the alveoli and the large bronchi, otherwise I can see no explanation for the fact that in emphysema the alveolar air (which in this patient was so rich in CO_2) should constitute such a small percentage of the tidal air when the rate of respiration and the minute-volume are normal or what conform to comfortable respiration and ventilation in a normal person.

In the case of Sam B. the alveolar air was rich in CO_2 and poor in oxygen. So the question naturally arose as to whether the cyanosis was due to an excess of CO_2 or diminution in oxygen.

It was formerly shown that a great increase in the partial pressure of oxygen did not modify the cyanosis nor the rate or apparent minute-volume. An oxygen tank was connected with a rubber bag which communicated with the Zuntz apparatus. In this manner the patient was enabled to breathe an atmosphere of pure oxygen. A sample was taken from the tank which yielded 93 per cent. of oxygen on analysis.

Sam B. had a respiratory rate of 22 per minute on this day (April 19, 1911), and maintained the same rate during the time the Zuntz specimen was collected. The time of collection was eight minutes. The minute-volume 8.431 liters. The sample contained 2.5 per cent. of CO_2. Another specimen was collected during 10 minutes and 40 seconds. The minute-volume was 9.510 liters. The respiratory rate varied between 20 and 25 per minute. The sample contained:

CO_2=2.9 per cent.; O_2=91.2 per cent.

In spite of the fact his alveoli were constantly filled with oxygen the cyanosis remained the same. We then took a Zuntz specimen from Sam B. when he was breathing atmospheric air with the following results:

Time of collection=8 min.
Minute-volume=7.895 liters.
Resp. rate=22 per min.
Zuntz specimen: CO_2=2.21 per cent.; O_2=19.5 per cent.
Alveolar air: CO_2=8.05 per cent.; O_2=12.3 per cent.

Sam B. was then instructed to breathe twelve times, as deeply and rapidly as he could. At the end of this forced breathing the alveolar air contained:

CO_2=6.79 per cent.; O_2=15.71 per cent.

During March, 1912, the opportunity was given to prove the interpretation given Sam B.'s cyanosis and emphysema, in a patient who entered the hospital with pronounced pulmonary emphysema, air hunger and cyanosis. The cyanosis was not nearly so intense as in the case of Sam B., but the lungs extended downward to the seventh, ninth and eleventh ribs, respectively, in the nipple, axillary and scapular lines. Furthermore, the central tendon of the diaphragm occupied a low position as evidenced by the downward displacement of the liver and the strong approximation of the hypochondria toward the median line during inspiration. Although the patient breathed laboriously, the respiratory rate was 15 per minute and the same rate was maintained while breathing through the Zuntz

valves. With the first trial, breathing was more laborious than when the apparatus was not used, consequently the minute-volume was large and a large amount of CO_2 was given off.

First experiment on A. S. March 29, 1912.

Time of collection=15 min.

Resp. rate per min.=14.

Minute-volume=10.15 liters.

The Zuntz specimen contained: CO_2=2.37 per cent.; O_2=18.1 per cent.

Alveolar air: CO_2=7.2 per cent.; O_2=14.3 per cent.

Respiratory quotient=0.79.

CO_2 per min.=0.241 liters.

Alveolar air=3.341 liters or 31.8 per cent. of the minute-volume.

After further trials A. S. learned to breathe through the apparatus with less effort. The following test is a specimen taken when the minute-volume was less, but the respiratory rate was the same, viz., 14 per minute.

Time of collection=11 minutes.

Resp. rate=14.

Minute-volume=8.059 liters.

The Zuntz specimen contained: CO_2=2.16 per cent.; O_2=18.7 per cent.

Alveolar air: CO_2=7.44 per cent.; O_2=12.44 per cent.

Total CO_2 per min.=0.174 liters.

Resp. quotient=0.9.

Alveolar air=2.339 liters or 29.7 per cent. of the minute-volume.

A few days later A. S. was much more comfortable. There was no cyanosis, but the respiratory rate remained the same as when the patient was cyanotic. The lower borders of the lungs were still at the seventh, ninth and eleventh ribs but the central tendon of the diaphragm was evidently not so low. Although the costal angle did not widen during inspiration there was not the strong approximation of the hypochondria as formerly, when cyanosis was present and the bronchial wheezing was more pronounced.

Third specimen from A. S., April 1, 1912.

While the Zuntz specimen was collected the patient breathed easily at the rate of 15 per minute.

Time of collection=13 minutes.

Resp. rate=15 per min.

Minute-volume=6.380 liters.

Zuntz specimen contained: CO_2=2.7 per cent.; O_2=18.4 per cent.

Alveolar air: CO_2=5.3 per cent.; O_2=15.5 per cent.

Resp. quotient=1.0 per cent.

CO_2 in minute-volume=0.172 liters.

Alveolar air=3.250 liters or 50.9 per cent. of the minute-volume.

When the third specimen was taken it must be observed that the respiratory rate was 15 as compared with 14 in the second specimen, and although the minute-volume in the third specimen was 6.380 L., as compared with 8.059 L. in the second specimen, the lung ventilation was much better, for the alveolar air constituted 50.9 per cent. of the minute-volume in the third specimen, and only 29.7 per cent. in the second specimen. Moreover, at the time the third specimen was taken the patient had no cyanosis and the alveolar air contained 5.3 per cent. of CO_2. When the second specimen was taken, cyanosis was pronounced and the alveolar air contained 7.44 per cent. CO_2. With a lesser minute-volume and the same respiratory rate there was much better lung ventilation.

The corollary from the experiment is that the respiratory rate and minute-volume (when studied apart from the CO_2 content of the tidal and alveolar air) are no guides for estimating the real ventilation of the lung when bronchiolar volume is a factor under consideration.

Another mode of reaction is exemplified in the following patient, Mrs. L., who entered Lakeside Hospital in June, 1912. This patient was a small, thin woman who weighed 100 pounds. For two years she had had dyspnea and could do very little work on account of her respiratory limitations. The heart was not enlarged, there were no signs of any cardiovascular disease, i. e., disease of the heart, or aortic or pulmonary circulation. There were no evidences of any mediastinal disease. The lungs were emphysematous and were situated at the seventh, tenth and eleventh ribs, respectively in the nipple, axillary and scapular lines. During inspiration the lower end of the sternum was retracted and the epigastrium protruded. The costal angle was not enlarged during inspiration. The costal borders to the eighth ribs did not diverge during inspiration, but below the eighth ribs there was marked respiratory divergence of the costal borders, so the base of the thoracic cage had a marked increase in the transverse diameter during inspiration. Mrs. L. was not cyanotic but she complained of air hunger and had a respiratory rate of 26 during her stay of three weeks in the hospital. There was no pronounced cyanosis but at times there was a suggestion of cyanosis in the cheeks, but the fingers, ears, or tongue never revealed any pronounced cyanosis. This patient evidently retained her normal respiratory threshold and therefore breathed rapidly to compensate for poor alveolar ventilation. Consequently in this patient there were two factors which contributed to lowering the percentage of alveolar air in the minute-volume of respired air, viz., emphysema and a rapid respiratory rate.

Zuntz specimens taken from Mrs. L. gave the following results:

Time of collection=9 minutes.

Resp. rate=25.11 per minute.

Minute-volume=7.800 L.

Sample of Zuntz specimen: CO_2=1.48 per cent.; O_2=19.3 per cent.

Alveolar air: CO_2=5.55 per cent.; O_2=13.44 per cent.

Respiratory quotient=0.8.

Alveolar air=26.6 per cent. of minute-volume.

CO_2 per minute=115 c.c.

Another specimen showed the alveolar air to equal 29.4 per cent. of the minute-volume.

These three patients all present some signs which they have in common, and in other respects they differ greatly. All had increased pulmonary volume, and, indeed, so far as objective signs of pulmonary volume are concerned, they all had their lungs in the maximum inspiratory volume. All had the characteristic skodaic resonance and all had the prolonged expiratory phase.

Sam B. had much more evidence of bronchitis than A. S. or Mrs. L. Sam B. was always cyanotic. A. S. had cyanosis only during his first week in the hospital. Mrs. L. never had pronounced cyanosis. Sam B. never suffered air hunger. A. S. had air hunger only during the period of cyanosis, and Mrs. L. was never free from air hunger.

If we compare the results in Mrs. L. with the results in A. S. there is at first glance apparently a marked inconsistency in the results obtained in the two patients.

The second specimen from A. S. gave a minute-volume of 8.059 liters. His alveolar air contained 7.44 per cent. of CO_2.

Mrs. L. showed in repeated tests a minute-volume a little less than eight liters. Her alveolar air always contained between 5.5 per cent. and 6 per cent. of CO_2. Her alveolar air ranged between 26 per cent. and 30 per cent. of the minute-volume. But A. S. was cyanotic at the test referred to, and Mrs. L. was never cyanotic. There was this difference, however—A. S. had a respiratory rate of only fifteen per minute, whereas Mrs. L. had a respiratory rate which was constantly from 23 to 26 per minute. That the lung ventilation was better in Mrs. L. must be granted because she was not cyanotic and her alveolar air had a CO_2 content of from 5.5 per cent. to 6 per cent. The fact that her alveolar air constantly composed only 26 to 30 per cent. of the minute-volume (as in A. S.) must then be due to the increased respiratory rate.

I have compared my own lung ventilation with the ventilation of emphysematous lungs when I employed the same respiratory rate and minute-volume which the emphysematous patients had, and found my alveolar air under these conditions represented 60 per cent. of the alveolar air as against 30 per cent. in the emphysematous patients. But this comparative test of respiratory rate and minute-volume and alveolar air was a comparison between a healthy person and emphysematous patients who were cyanotic. I therefore wished to compare my lung ventilation with that of an emphysematous patient who was not cyanotic.

I then took a Zuntz specimen from myself when I breathed twenty-five times per minute and endeavored to breathe so that the minute-volume would be the same as in Mrs. L. This was accomplished by setting up a mirror before the dial of the spirometer so that the excursion of the indicator could be seen and thus, at will, the amount of each respiratory excursion could be made to conform to the desired minute-volume. An assistant beat time so that the number of respirations could be timed for exactly 25 respirations per minute. Thus the minute-volume respiration of Mrs. L. was accurately imitated in my own breathing. While this artificial respiratory rate and minute-volume were maintained it was desirable also to know what the CO_2 content of the alveolar air might be. For this purpose the mouth-piece of the Zuntz apparatus was fitted with a lateral opening through which a sample of alveolar air could be procured at the end of the experiment. It was necessary to know the oxygen and carbonic acid content, not only for estimating the proportion of alveolar air to the minute-volume of air, but also to see if the percentage of carbonic acid in the alveolar air conformed to the sense of air hunger which prevailed during the time the Zuntz specimen was being taken. The alveolar air was taken on the end of the last expiration of the seven minutes during which the Zuntz specimen was taken.

Time of collection=7 min.
Resp. rate=25 per min.
Min.-vol.=7.400 L.
Resp. quot.=0.66.
Per cent. of alv. air of the min. vol.=39.7 per cent.
Zuntz specimen: CO_2=2.6 per cent.; O_2=17.3 per cent.
Alveolar air: CO_2=6.7 per cent.; O_2=13.2 per cent.

Another trial was made during which the sense of air hunger was not so severe as during the above test, but the sense of air hunger was pronounced.

Time of collection=8 min.
Resp. rate=25 per min.
Min.-vol.=7.570 L.
Resp. quot.=0.65.
Per cent. of alv. air of the min.-vol.=44.9.
Zuntz specimen: CO_2=2.8 per cent.; O_2=17.0 per cent.
Alveolar air: CO_2=6.27 per cent.; O_2=13.73 per cent.

When the results are compared with those of Mrs. L. it will be noted that the alveolar air represented a larger portion of the minute-volume than in the case of Mrs. L. and although my sense of air hunger was pronounced, as was also quite evident in Mrs. L., my alveolar air at the end of the experiment contained 6.7 per cent. and 6.2 per cent. of CO_2. Whereas Mrs. L.'s alveolar air contained only 5.5 per cent. This seemed too low to be consistent with her sense of air hunger, the degree of emphysema, and also the suggestion of cyanosis in her face, which amounted to a slightly dusky hue, although as has been stated there never was pronounced cyanosis of the fingers, ears or tongue. The estimates of Mrs. L.'s alveolar air compared with her minute-volume of air always proved the lung ventilation to be poor. As has been shown, when I employed the same respiratory rate and minute-volume as Mrs. L., my alveolar air represented 10 per cent. more of the minute-volume than was the case with Mrs. L., although the percentage of CO_2 in my alveolar air was higher than Mrs. L. In spite of this comparison it never seemed to me that we quite got the alveolar air of Mrs. L. The degree of emphysema and air hunger always seemed inconsistent with such a moderate elevation of partial pressure in the CO_2 of her alveolar air. From our former experiences with emphysema, too, it seemed reasonable to expect a better tolerance of such an elevation of CO_2 content of the alveolar air, in a patient who had emphysema continuously for two years. I mean by this that the sense of air hunger was disproportionately great for the CO_2 content of the alveolar air as estimated from a specimen of air procured at the end of a strong, quick, voluntary expiration.

Mrs. L. was a frail woman with a thin thorax which could be easily compressed. As we thought the real alveolar air may be better procured by compressing the thorax at the same time a voluntary expiratory effort was made, the following experiments were then made:

A Zuntz specimen was taken for 11 minutes.
The minute-volume was 7.522 liters.
Respiratory rate 22½ per min.

Zuntz specimen: CO_2=1.9 per cent.; O_2=19.0 per cent.

The alveolar air was then taken at the end of a voluntary expiration. The first specimen contained 5.7 per cent. of CO_2. The second specimen 6.1 per cent. of CO_2.

The patient breathed through the tube used in procuring alveolar air and then as she was instructed to blow, her nose was closed by one assistant, another seated behind the patient forcibly compressed the thorax as the forced expiration was made, and immediately the specimen of air was taken. This was all done so quickly that the time factor could not be responsible for a high CO_2 content. The specimen was procured as promptly as at other times when there was no compression of the thorax employed. The alveolar air procured in this manner had a CO_2 content of 6.7 per cent. which seemed quite consistent with the whole clinical picture.

The patient, A. S., had a CO_2 content of 7.4 per cent. in his alveolar air when he was cyanotic and 5.3 per cent. a few days later when he was not cyanotic.

If the percentage of alveolar air is estimated on the basis of 6.7 per cent. CO_2, then the alveolar air will constitute 28.3 per cent. of the minute-volume. If the estimate is made on the basis of 6.1 per cent., the alveolar air constitutes 31.1 per cent. of the minute-volume.

This method of compressing the thorax was employed in the case of Sam B., whose alveolar air at the time contained 8.3 per cent. of CO_2, and the results obtained were the same as when no compression was employed. His thorax was unyielding and the trunk muscles were powerful.

The same results as in Sam B. were obtained in two healthy well-muscled men. It seems probable that in the case of Mrs. L. 6.7 per cent. more nearly represents the CO_2 content of her alveolar air than 5.3 per cent., or 6.1 per cent., which were the minimum and maximum percentages obtained in a dozen analyses, made at different times.

This method of estimating the lung ventilation proved to be of service in studying the case of a man 71 years old who gave a history of air hunger which existed two months before entering Lakeside Hospital.

This patient, L. S., was a powerful man with a large and very resistant thoracic cage. The only complaint the patient had was constant air hunger and frequent attacks of hyperpnea which wakened him at night. There was no cyanosis nor evidences of any cardiovascular disease. There was marked retraction of the costal borders and narrowing of the costal angle during inspiration. The lungs were voluminous. The finger nails were ridged and he gave a very clear history of gout which had been diagnosed by several physicians.

At the base of the right thorax in the axillary line there was movable dulness which was not pronounced, but gave rise to the suspicion of fluid in the right pleural cavity. Although the lungs were voluminous (at the ninth rib in the axillary lines), and the respiratory movements of the hypochondria betrayed a low position of the central tendon of the diaphragm, yet there were no signs of bronchitis.

The real question in this case was to account for the low position of the central tendon of the diaphragm. The CO_2 of his alveolar air was first determined from specimens procured at the end of a forced expiration and found to be 3.7 per cent., 3.8 per cent. and 3.9 per cent. in three specimens. Compression was then employed at the end of the expiration and the CO_2 content was 3.5 per cent., 3.7 per cent. and 4.2 per cent. in three specimens.

A Zuntz specimen was then taken for nine minutes.

The minute-vol.=7.405 L.

The rate of respiration=16 per min.

The air sample: CO_2=1.9 per cent.; O_2=19.0 per cent.

Alveolar air taken directly after the Zuntz specimen was finished gave a CO_2 content of 3.2 per cent. and 3.3 per cent. in two specimens.

The alveolar air equalled 58 per cent. of the minute-volume; therefore the low position of the diaphragm could not be due to emphysema of bronchial origin.

A skiagram of the thorax was then made and a tumor in the mediastinum directly behind the heart was clearly definable which displaced the central tendon downward. An exploratory needle was then inserted and a thin layer of fluid was located at the base of the right thorax. The fluid was not bloody, but contained a few red cells and many mononuclear cells. The patient left the hospital, but the skiagram justified the diagnosis of a mediastinal tumor which simulated bronchial emphysema by its displacement of the central tendon of the diaphragm. Had not the estimates of the minute-volume and alveolar air been made we would have overlooked the real disease and regarded the whole difficulty as bronchial emphysema with nocturnal asthma.

In the cases of Sam B. and Mrs. L. atropin and epinephrin (adrenalin) were given subcutaneously to see if the percentage of CO_2 in their alveolar air could be modified. One thirty-fifth grain of atropin sulphate and 20 minims of 1:1,000 epinephrin were given in each case. The CO_2 content of the alveolar air remained the same in both patients before and after the use of both atropin and epinephrin.

CONCLUSIONS

The essential result of these observations of pulmonary emphysema is the direct evidence that in emphysema the patient suffers from an impaired alveolar ventilation of the lung and not from an impairment of the lung as the organ of external respiration. Furthermore, the evidence seems very conclusive that the alveolar air constitutes a very diminished part of the minute-volume of air. So the minute-volume in any given case of emphysema is not a measure of alveolar ventilation. This diminution of the proportion of alveolar air must be due to an increase of the dead space. How can we account for an increase of the dead space in pulmonary emphysema? Can the increase of the dead space be explained best by bronchiolar spasm, bronchiolar atony, or swelling of the bronchial mucosa? Bronchiolar atony, that is, an elongation and broadening of the bronchioles, seems the most consistent with an increase of the dead space. Bronchiolar spasm or swelling of the bronchial mucosa could give an increase of the dead space only by an inspiratory enlargement of that portion of the air passage which lies between the alveoli and the larynx.[4]

I hope in the near future to present the evidence from some completed animal experiments which will throw light on this question.

In conclusion I wish to thank Dr. Chauncy Wycoff, former resident of Lakeside Hospital, and Dr. L. H. Taylor, resident physician at Lakeside Hospital, for their valuable assistance in this work.

700 Rose Building.

4. Douglas and Haldane suggest the neuromuscular activity of the bronchiolar system as a source for enlarging and diminishing the dead space under physiological conditions. Jour. Physiol., Oct. 22, 1912, No. 4.

A FURTHER STUDY OF THE VENTILATION OF SLEEPING CARS (THE STEEL CAR)*

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CHICAGO

Two years ago I presented before the American Public Health Association the results of a study of the ventilation of sleeping cars.[1] An attempt was made to determine the amount of fresh air which enters the running car under various conditions of operation, the places of entrance of the air, its distribution, and the general direction of its currents. Two plans of ventilating were considered in that study, which were called "natural ventilation" and "ventilation by exhaustion."

The essential architectural features of the standard American railway car are, as they concern the question under discussion, that it contains one long room with end doors opening to vestibules, and side windows, and was originally intended to receive its air supply through a row of small windows set in near the roof line on either side and called deck-sashes. Part of the cars investigated in the study referred to were ventilated in this way, as are still the vast majority of the railway cars in this country. Since natural forces alone are depended on to induce air interchange, this plan was referred to as "natural ventilation."

To the majority of the cars investigated there had been applied a device[2] intended to remove air through certain of these upper windows, or deck-sashes, by a suction effect dependent on train motion, all other deck-sashes remaining closed. This plan was called "ventilation by exhaustion." It would tend to reverse the fresh air currents from a downward to an upward direction; instead of air being admitted at the top by natural forces through openings provided for that purpose and allowed to find its own way out, it would be removed at the top by artificial devices and left to find its own way in. That the exhaust apparatus actually did what it was intended to do was easily determined by means of the anemometer. It was found that each of these exhaust ventilators would remove about 15,000 cubic feet of air each hour at a forty-mile

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*Manuscript submitted for publication Oct. 29, 1912.

1. Crowder: A Study of the Ventilation of Sleeping Cars, THE ARCHIVES INT. MED., 1911, vii, 85.

2. The Garland Ventilator. This is described in the Railway Age, 1906, xli, 847, and in the Railway Age-Gazette, 1910, l, 1757.

train speed. Six to eight of them were applied to each car. The problem then was to determine the manner of entrance of the air, the general course of its currents, and the efficiency of the device in maintaining a fresh air supply to the breathing zone for the passengers and to the occupied berth, and to compare the results obtained by the two methods of ventilation. This was done by determining the respiratory contamination of the air of the car as represented by the proportion of carbon dioxid in the air. It is well known that from such determinations air supplies can be computed[3] with considerable accuracy.

The results of a large number of observations showed that by the application of this exhaust device the active ventilation of the body and

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3. The problem is simple. The air supply is inversely as the respiratory contamination. It may be computed from the following equation:

$$A = \frac{vp}{x - N}$$

where v = the CO_2 produced by one person (cu. ft. per hour),
p = the number of people in the car,
x = the proportion of CO_2 found in the air of the car,
N = the proportion of CO_2 in the outside air,
and A = the air supply to the car (cu. ft. per hour).

It is seen that vp is the CO_2 produced by the occupants and x—N is the respiratory contamination. We may substitute known values for the letters v and N in the above equation. The amount of CO_2 produced by one person will average very close to 0.6 cu. ft. per hour, and the average proportion of CO_2 in the air surrounding trains has been found to be very close to 0.0004, or 4 parts in 10,000. Making the substitution the equation becomes:

$$A = \frac{0.6\,p}{x - 0.0004}$$

Completing the computation of air supply for various assumed proportions of CO_2 the results would be, when the space is occupied by one person only, i. e., when p is the unit 1, as follows:

$CO_2 = 0.0020$ (resp. contam. $= 0.0016$), hourly air supply = 375 cu. ft.
$CO_2 = 0.0016$ (resp. contam. $= 0.0012$), hourly air supply = 500 cu. ft.
$CO_2 = 0.0012$ (resp. contam. $= 0.0008$), hourly air supply = 750 cu. ft.
$CO_2 = 0.0010$ (resp. contam. $= 0.0006$), hourly air supply = 1,000 cu. ft.
$CO_2 = 0.0009$ (resp. contam. $= 0.0005$), hourly air supply = 1,200 cu. ft.
$CO_2 = 0.0008$ (resp. contam. $= 0.0004$), hourly air supply = 1,500 cu. ft.
$CO_2 = 0.0007$ (resp. contam. $= 0.0003$), hourly air supply = 2,000 cu. ft.
$CO_2 = 0.0006$ (resp. contam. $= 0.0002$), hourly air supply = 3,000 cu. ft.
$CO_2 = 0.0005$ (resp. contam. $= 0.0001$), hourly air supply = 6,000 cu. ft.

These same figures apply to a room with any number of occupants provided we add "per person" after "hourly air supply." In order for the air to maintain a constant respiratory contamination the volume supplied must be multiplied as often as we multiply the occupants—the air-supply must maintain a constant ratio to the CO_2 produced. Each person will contaminate 1,000 cu. ft. of air per hour to the extent of 6 parts of CO_2 in 10,000 of air (and the total CO_2 will be 10 parts in 10,000). One person will need simply the 1,000 cu. ft. per hour if the contamination is to be held at this level; fifty will need 1,000 cu. ft. each, or 50,000 cu. ft. The estimation of air supply to a car must be based on the total amount of CO_2 produced by all of its occupants.

berths of a sleeping car is considerably increased over and above what may be expected from the natural forces of the wind through the open deck-sashes, and that the flow of fresh air into the car is more regular and better distributed. The many crevices about doors and windows act as intakes and the trend of the currents is of course upward. The respiratory contamination of the air of the breathing zone and of the occupied berth remains almost constantly low. Carbon dioxid reaches a proportion of ten parts in 10,000 of air with relative rarity; and the computed fresh air supply averages about 2,000 cubic feet per hour for each berth and about 40,000 cubic feet per hour for the car.

With the adoption of this exhaust system of ventilation as a standard of construction the deck-sashes cease to perform any important function. Indeed, they may become a direct hindrance to the most efficient operation of the device. They are of necessity, from their location and the method of their operation, loose fitting windows which furnish large crevices for air leakage. Since these crevices are located very near the outlets of the exhaust ventilators, the air entering through them is liable to be drawn directly out again and to play no part in effecting air renewal of the breathing zone. Furthermore, it tends to prevent air being drawn upward from the window crevices located below and the effective renewal of the air of the lower levels. That such short-circuiting does take place was shown in the study referred to: whereas by actual measure, some 80,000 cubic feet of air leaves the car each hour through the exhaust ventilator openings, there is only about 40,000, as computed from CO_2 determinations, supplied to the breathing zone. The difference between the aeration of the breathing zone and the total air supply is not so great, however, as these figures would seem to indicate, since it is well known that CO_2 determinations generally give an air supply which is under rather than over the actual. Furthermore, the estimate of total air outflow is here based on a constant forty-mile speed, whereas the estimates from CO_2 include all rates of running as well as short stops.

The study from which the foregoing is drawn was made on the standard Pullman sleeping car of wooden construction. The exhaust ventilator considered was applied to cars which had been previously in service and had been originally ventilated by the natural or deck-sash method. Since the completion of that study the all-steel sleeping car has come into extensive use. These cars are all equipped with exhaust ventilators in the building; and for the reasons stated above the deck-sashes are omitted, or, if not entirely omitted, they are reduced from twenty-four to four, and these four are very small. Only electricity is used for lighting; this avoids the necessity of making openings through the roof to carry away the combustion gases of burning lights. The upper portion of the car is almost entirely free from natural openings.

It is therefore readily seen that whatever air enters these cars must come from crevices about windows and doors located low down. From this it would naturally follow that the lower levels of the car receive a larger air supply than with the older type of construction. It is not considered a matter of great hygienic importance whether they do or do not; no increase in the air supply is demanded on hygienic grounds; but in order to have some adequate information as to what actually does take place and to be able to make accurate comparisons, a series of thirty-six steel cars were investigated during the first two months of 1912.

The methods used in the investigation of these cars are the same as those previously employed. They are fully outlined in the original paper,[1] to which those interested are referred. Samples of the air to be examined were collected in glass-stoppered bottles, sealed, and were analyzed in the Petterson-Palmquist apparatus for the determination of carbon dioxid. Air was collected from the center aisle, in order to determine the respiratory contamination of the general air of the car, and from lower and upper berths in order to determine the respiratory contamination of the air within them. From these contaminations air supplies have been computed as has been previously explained.[2]

All the observations in the cars included in the present series were made during the night, after the passengers had retired. The time ranged from 11:00 p. m. to early morning. The outside temperature varied from 0 F. to 36 F.; it was generally as low as 20 F. Samples were taken as nearly simultaneously as possible in the aisle and in from three to six berths; samples from the same places were repeated at approximately fifteen minute intervals for one or two hours. This was done in order to obtain general averages, which are more important and give much more dependable information of the condition of the air than single observations or short series. From the latter erroneous conclusions are very likely to be drawn. It must be recognized that in any running car the conditions are liable to rapid and relatively great variation. Minimum actual rates of air supply, hence degrees of respiratory contamination, alternate with maximum actual rates; and these minimums and maximums may lie a considerable distance apart. They represent temporary and local, not continuous and general, conditions. General averages are much more significant.

GENERAL RESULTS

In Table 1 are assembled the more important items concerning the general air of the cars examined. The air tests recorded in this table refer only to the samples collected from the car body, and not to those collected from the berths. The air supply as computed is expressed to

the nearest thousand in terms of cubic feet per car per hour. It is that volume which would keep the CO_2 at the average proportion found in the air of the car if the number of occupants did not change.

TABLE 1.—DETERMINATIONS OF THE VENTILATION OF STEEL SLEEPING CARS EQUIPPED WITH EXHAUST VENTILATORS

Experiment	Name of Car	Temp. F.		No. of People in Car	CO_2 per 10,000 of Air				Approx. Hourly Air Supply
					No. of Tests	Average	Extremes		
		Out	In				Min.	Max.	
1	Cresheim	12	52	16	6	5.50	4.5	6.0	64,000
2	Millard*	36	60	15	8	5.25	4.5	6.5	72,000
3	Brightwood* ...	10	56	15	7	6.00	5.0	7.0	45,000
4	Thurston	30	56	28	7	6.79	6.0	8.5	60,000
5	Sparks†	34	60	18	10	5.45	4.5	7.0	74,000
6	Cresheim*	20	58	19	11	5.82	5.0	7.5	70,000
7	Parkerton*	24	61	10	9	5.28	4.5	6.0	47,000
8	Bridgeport*	24	60	10	8	5.56	4.5	6.5	38,000
9	Millard‡	26	59	14	9	4.77	4.5	5.5	109,000
10	Lemay‡	26	60	15	9	4.72	4.5	5.0	125,000
11	Amsden	30	60	18	7	6.00	5.0	8.0	54,000
12	Walworth	30	63	17	7	5.71	5.0	8.0	59,000
13	Thurston	24	54	19	7	6.57	6.0	7.0	44,000
14	Moorfield	24	60	18	7	5.93	5.5	6.5	56,000
15	Bogero	20	58	12	7	5.21	4.5	5.5	59,000
16	Somena	20	58	16	7	5.50	5.0	6.0	64,000
17	Wawa	30	62	18	9	6.39	5.5	9.5	45,000
18	Nepperhan	24	63	18	7	5.79	5.0	7.0	60,000
19	Monteith	24	58	16	7	6.36	5.5	7.0	41,000
20	Ship Road	6	60	12	7	5.14	4.5	6.0	63,000
21	Hyndman	6	60	8	7	4.79	4.5	5.5	57,000
22	Thurston§	6	58	26	7	7.21	6.0	9.5	49,000
23	Roseton§	6	60	22	4	8.13	7.5	8.5	32,000
24	Colfax	16	60	16	6	5.92	5.0	8.0	50,000
25	Dorrance	16	60	17	5	5.40	5.0	5.5	72,000
26	Onchiota	24	60	15	5	5.20	4.5	6.0	75,000
27	Canfield	24	60	21	5	7.10	6.0	8.0	41,000
28	Carrothers	0	58	15	6	5.83	5.0	6.5	49,000
29	Wawa	0	58	14	6	6.66	5.5	8.0	33,000
30	Elkland	8	56	20	5	6.30	5.5	7.5	52,000
31	Onchiota	8	56	15	6	6.25	5.5	7.0	40,000
32	Middletown	8	68	12	3	5.33	5.0	5.5	54,000
33	Josslyn	20	62	15	5	5.30	5.0	5.5	69,000
34	Halleck	20	62	12	6	5.08	4.5	6.0	67,000
35	Millard	12	58	12	7	5.07	5.0	5.5	74,000
36	Henefer	12	60	10	7	4.93	4.5	6.0	65,000
	36 cars	..	..	16.2	246	5.78	4.5	9.5	54,600

*Drop-sashes of end doors open 3 inches (see note 4).
†Drop-sash of rear door open 12 inches (see note 4).
‡Drop-sashes of end doors open 24 inches (see note 4).
§Train running directly with a strong wind.

The observations from which Table 1 is compiled may be summarized as follows:

Cars examined	36	
Average number of occupants	16.2	
Number of air samples analyzed	246	
Average number of samples per car	6.86	
Average carbon dioxid	5.78:10,000	
Highest average CO_2 in any car	8.13:10,000	
Lowest average CO_2 in any car	4.72:10,000	
Highest CO_2 in any sample	9.5 :10,000	
Lowest CO_2 in any sample	4.5 :10,000	
Number samples showing CO_2 over 10:10,000	0	(0.00%)
Number samples showing CO_2 over 8:10,000	5	(2.03%)
Number samples showing CO_2 over 7:10,000	20	(8.13%)
Number samples showing CO_2 over 6:10,000	56	(22.76%)
Number samples showing CO_2 6 or less:10,000	190	(77.24%)
Average hourly air supply per car, cu. ft	54,600	
Highest hourly air supply for any car, cu. ft	125,000	
Highest excepting Nos. 9 and 10,[4] cu. ft	75,000	
Average excepting Nos. 9 and 10,[4] cu. ft	53,000	
Lowest hourly air supply for any car, cu. ft	32,000	
Number of cars showing less than 40,000 cu. ft. per hour, 3		(8.33%)

The average air supply to the breathing zone of the steel sleeping car, as computed from the average proportion of CO_2 and the average number of occupants in the thirty-six cars examined, is found to be approximately 54,600 cubic feet per hour, as above stated; or, in those cars kept entirely closed, even to drop-sashes in the end doors,[4] 53,000 cubic feet per hour.

4. The end doors of the car are fitted with small sliding windows, which may be lowered from the top and held at any level by a catch. These windows are commonly referred to as "drop-sashes." In regular service it is customary to maintain a variable opening of these windows in order to facilitate the entrance of fresh air from the vestibule. During the first ten experiments they were let alone as found; in all later experiments they were purposely kept closed while observations were being made.

An examination of Table 1 will show that only twice, namely, in Experiments 9 and 10, was the air supply markedly affected by these open drop-sashes, and in these cars the sashes were opened widely. These two cars were on the same train and air samples from the two were collected at approximately the same time. The air supply in these two instances is so greatly increased as to show a considerably higher average air supply and lower CO_2 for the small group of eight cars which had some opening of the drop-sashes, than for the others in which there was no opening at all. The averages for the eight cars are: CO_2, 5.34; occupants, 14.7; equivalent air supply, 65,900 cu. ft. per hour. The averages for all other cars, which had no openings in the end doors, are: CO_2, 5.90; occupants, 16.8; equivalent air supply, 53,000 cu. ft. per hour. Leaving out of consideration only Nos. 9 and 10 the other thirty-four cars show the following averages: CO_2 5.85; occupants 16.3; air supply 53,000 cu. ft. per hour. It is seen that the final results are affected only slightly by including in the general averages the findings in these two cars.

The general averages as above noted and as used throughout are found by adding together all single observations and dividing by the total number, and not by adding the car averages. The two methods will often give slightly different results, but the difference has never been found great enough to make material changes.

TABLE 2.—DETERMINATIONS OF THE VENTILATION OF THE LOWER BERTHS OF STEEL SLEEPING CARS EQUIPPED WITH EXHAUST VENTILATORS

Experiment	Name of Car	Temp. F.		No. of People in Car	Aisle			Lower Berths							Approx. Hourly Air Supply per Berth
		Out	In		Average CO_2 per 10,000	Extremes		No. Examined	Total No. of Tests	Average CO_2 per 10,000	Extremes		Tests Over 12:10,000	Tests Over 10:10,000	
						Min.	Max.				Min.	Max.			
1	Cresheim ...	12	52	16	5.50	4.5	6.0	4	24	5.73	4.5	7.0	0	0	3470
2	Millard*	36	60	15	5.25	4.5	6.5	4	32	6.64	4.5	10.0	0	0	2270
3	Brightwood*	10	56	15	6.00	5.0	7.0	4	28	6.66	5.0	9.0	0	0	2250
4	Thurston ...	30	56	28	6.79	6.0	8.5	3	21	7.12	5.5	10.5	0	1	1920
5	Sparks†	34	60	18	5.45	4.5	7.0	3	30	6.18	4.5	9.5	0	0	2750
6	Cresheim* ...	20	58	19	5.82	5.0	7.5	4	44	6.69	5.0	9.5	0	0	2230
7	Parkerton* ..	24	61	10	5.28	4.5	6.0	3	27	6.07	4.5	8.0	0	0	2900
8	Bridgeport* ..	24	60	10	5.56	4.5	6.5	3	22	7.05	5.0	9.0	0	0	1970
9	Millard‡	26	59	14	4.77	4.5	5.5	3	27	6.06	5.0	10.0	0	0	2910
10	Lemay‡	26	60	15	4.72	4.5	5.5	2	18	6.06	5.0	7.5	0	0	2910
11	Amsden	30	60	18	6.00	5.0	8.0	2	14	7.36	5.9	14.0	1	1	1790
12	Walworth ...	30	63	17	5.71	5.0	8.0	3	21	7.64	4.5	14.0	1	4	1650
13	Thurston	24	54	19	6.57	6.0	7.0	3	21	9.02	7.5	10.5	0	1	1200
14	Moorfield	24	60	18	5.93	5.5	6.5	3	21	6.62	6.0	9.0	0	0	2290
15	Bogero	20	58	12	5.21	4.5	5.5	4	28	6.41	5.0	8.0	0	0	2470
16	Somena	20	58	16	5.50	5.0	6.0	2	14	6.64	5.5	8.0	0	0	2270
17	Wawa	30	62	18	6.39	5.5	9.5	3	27	7.55	5.0	11.5	0	2	1690
18	Nepperhan ...	24	63	18	5.79	5.0	7.0	3	21	6.09	5.0	7.5	0	0	2870
19	Monteith	24	58	16	6.36	5.5	7.0	4	28	7.52	5.5	11.0	0	2	1700
20	Ship Road ...	6	60	12	5.14	4.5	6.0	4	28	6.33	4.5	8.5	0	0	2570
21	Hyndman ...	6	60	8	4.79	4.5	5.5	4	28	6.36	4.5	11.5	0	1	2540
22	Thurston§	6	58	26	7.21	6.0	9.5	4	28	9.25	7.0	12.5	1	5	1140
23	Rosetons§	6	60	22	8.13	7.5	8.5	4	16	9.22	7.5	10.5	0	1	1150
24	Colfax	16	60	16	5.92	5.0	8.0	4	24	7.01	5.5	10.0	0	0	1990
25	Dorrance	16	60	17	5.40	5.0	5.5	4	20	5.85	5.5	6.5	0	0	3240
26	Onchiota	24	60	15	5.20	4.5	6.0	4	20	5.55	4.5	6.5	0	0	3870
27	Canfield	24	60	21	7.10	6.0	8.0	4	20	7.81	5.0	9.5	0	0	1570
28	Carrothers ...	0	58	15	5.83	5.0	6.5	4	24	6.31	5.0	9.0	0	0	2600
29	Wawa	0	58	14	6.66	5.5	8.0	4	24	6.93	5.0	9.0	0	0	2050
30	Elkland	8	56	20	6.30	5.5	7.5	4	20	7.01	5.0	9.0	0	0	1990
31	Onchiota	8	56	15	6.25	5.5	7.0	4	24	6.89	5.5	8.0	0	0	2080
32	Middletown ..	8	68	12	5.33	5.0	5.5	4	12	6.50	5.5	7.5	0	0	2400
33	Josslyn	20	62	15	5.30	5.0	5.5	4	20	5.91	5.0	6.5	0	0	3140
34	Halleck	20	62	12	5.08	4.5	6.0	4	24	6.85	5.0	10.0	0	0	2110
35	Millard	12	58	12	5.07	5.0	5.5	4	28	6.21	5.0	7.5	0	0	2720
36	Henefer	12	60	10	4.93	4.5	6.0	4	28	5.91	5.0	8.5	0	0	3140
	36 cars			16.2	5.78	4.5	9.5	128	856	6.76	4.5	14.0	3	18	2170

*Drop-sashes of end doors open 3 inches (see Note 4).

†Drop-sash of rear door open 12 inches (see Note 4).

‡Drop-sashes of end doors open 24 inches (see Note 4).

§Train running directly with a strong wind.

This compares with 40,600 cubic feet per hour for the older type of car, equipped with the same ventilating device, but maintaining the deck-sash construction, and with 28,300 cubic feet per hour for cars having the ordinary deck-sash ventilation. The results in the steel car are also more uniform and more regular, as will be found by consulting the detailed results of the first group of experiments.[1] The complete comparative averages may be grouped as follows:

A. Wood Cars (with Deck-Sash Construction)

1. Natural ventilation (deck-sash method)
   a. Fully closed car ..... 18,500 cu. ft. per hour
   b. With open deck-sashes ..... 28,300 cu. ft. per hour
   c. With open deck-sashes and open end doors ..... 40,700 cu. ft. per hour
2. Exhaust ventilation (the exhaust method)
   a. Fully closed car ..... 40,600 cu. ft. per hour
   b. With open doors ..... 57,900 cu. ft. per hour

B. Steel Cars (Constructed Without Deck-Sashes)

Exhaust ventilation
   a. Fully closed car ..... 53,000 cu. ft. per hour
   b. With open drop-sashes in end doors[4] ..... 65,900 cu. ft. per hour

Any or all of these figures might be changed by longer series of observations. For most of the groups it is believed a sufficient number have been made to insure the relative correctness of the results obtained.

THE LOWER BERTH

In Table 2 are assembled the observations in lower berths and comparisons with the air of the aisle taken at the same time. It will be noted that the experiments recorded in this table are the same as those presented in Table 1, and that they cover all the cars investigated. The air supply per berth, as computed, is the number of cubic feet which must be supplied to one person each hour in order to maintain the CO_2 at the average proportion found. The berths included in this list were each occupied by one adult.

The observations from which Table 2 is compiled may be summarized as follows:

Cars in which lower berths were examined	36
Number of lower berths examined	128
Average number of lower berths per car	3.56
Total number of air samples from lower berths	856
Average number of lower berth samples per car	23.78
Average number of samples per berth	6.53
Average CO_2 in air of car body	5.78:10,000
Average CO_2 in air of lower berths	6.76:10,000
Highest average CO_2 in lower berths of any car	9.25:10,000
Lowest average CO_2 in lower berths of any car	5.55:10,000
Highest CO_2 in any lower berth sample	14 :10,000
Lowest CO_2 in any lower berth sample	4.5 :10,000

Number L. B. samples showing CO_2 over	12:10,000	3 (0.35%)
Number L. B. samples showing CO_2 over	10:10,000	18 (2.10%)
Number L. B. samples showing CO_2 over	8:10,000	137 (16.00%)
Number L. B. samples showing CO_2 over	7:10,000	238 (27.80%)
Number L. B. samples showing CO_2 over	6:10,000	476 (55.61%)
Number L. B. samples showing CO_2 6 or less	10,000[5]	380 (44.39%)
Number L. B. with higher CO_2 than aisle at same time		658 (76.87%)
Number L. B. with lower CO_2 than aisle at same time		68 (7.95%)
Number L. B. with CO_2 equal to aisle at same time		130 (15.19%)
Average hourly air supply per lower berth, cu. ft		2170
Highest average hourly air supply to L. B. of any car, cu. ft		3870
Lowest average hourly air supply to L. B. of any car, cu. ft		1140
Number cars showing average of less than 1500 cu. ft. per L. B. per hour,[6]		(8.33%)

On the basis of 856 carbon dioxid determinations in the air of 126 lower berths in thirty-six steel sleeping cars equipped with exhaust ventilators, the average air supply per berth is found to be approximately 2,170 cubic feet per hour. This compares with 2,030 cubic feet for the lower berths of the older type of cars equipped with the same ventilating device, and with 1,390 cubic feet in cars ventilated by the deck-sash method.[1]

THE UPPER BERTH

Table 3 records the observations made in upper berths and comparisons with the air of the aisle taken at the same time. The items included are the same as those for the lower berths in the preceding table.

The results of examination of upper berths may be summarized as follows:

Cars in which upper berths were examined	21
Number of upper berths examined	30
Average number of upper berths per car	1.43
Total number of air samples from upper berths	207
Average number of upper berth samples per car	9.86
Average number of samples per berth	6.9
Average CO_2 in air of car body	5.86:10,000
Average CO_2 in air of upper berths	7.00:10,000
Highest average CO_2 in upper berths of any car	8.70:10,000
Lowest average CO_2 in upper berths of any car	5.44:10,000
Highest CO_2 in any upper berth sample	11.5 :10,000
Lowest CO_2 in any upper berth sample	4.5 :10,000

5. These figures may be converted into terms of air supply. For every proportion of CO_2 in the air there is an equivalent hourly air supply. When the CO_2 is 6 per 10,000 there is a dilution of the expired air which would be maintained by 3,000 cubic feet of fresh air per hour; when the proportion of CO_2 is less than 6 per 10,000 there must be more than 3,000 cubic feet per hour. The conversion gives the following results:

Lower berth tests showing 3000 or more cu. ft. per hour	44.39%
Lower berth tests showing 2000 or more cu. ft. per hour	72.20%
Lower berth tests showing 1500 or more cu. ft. per hour	84.00%
Lower berth tests showing 1000 or more cu. ft. per hour	97.90%
Lower berth tests showing 750 or more cu. ft. per hour	99.65%

6. These cars were Nos. 13, 22 and 23. The last two were on the same train and samples were taken in them at approximately the same time. The train was running directly with a strong wind. Nos. 13 and 22 are the same car, on different trips.

Number U. B. samples showing CO_2 over 12:10,000 ..... 0 (0.00%)
Number U. B. samples showing CO_2 over 10:10,000 ..... 5 (2.42%)
Number U. B. samples showing CO_2 over 8:10,000 ..... 34 (16.43%)
Number U. B. samples showing CO_2 over 7:10,000 ..... 83 (40.10%)
Number U. B. samples showing CO_2 over 6:10,000 ..... 139 (67.15%)
Number U. B. samples showing CO_2 6 or less :10,000[7] 68 (32.84%)
Number U. B. with higher CO_2 than aisle at same time 182 (87.92%)
Number U. B. with lower CO_2 than aisle at same time 13 (6.28%)
Number U. B. with CO_2 equal to aisle at same time 12 (5.80%)

Average hourly air supply per upper berth, cu. ft 2000
Highest average hourly air supply for U. B. of any car, cu. ft 4170
Lowest average hourly air supply for U. B. of any car, cu. ft 1280

Number of cars showing average of less than 1,500 cu. ft. per U. B. per hour, 2 ..... (9.52%)

TABLE 3.—DETERMINATIONS OF THE VENTILATION OF THE UPPER BERTHS OF STEEL SLEEPING CARS EQUIPPED WITH EXHAUST VENTILATORS

Experiment	Name of Car	Temp. F.		No. of People in Car	Aisle			Upper Berths							Approx. Hourly Air Supply per Berth
		Out	In		Average CO_2 per 10,000	Extremes		No. Examined	Total No. of Tests	Average CO_2 per 10,000	Extremes		Tests Over 12:10,000	Tests Over 10:10,000	
						Min.	Max.				Min.	Max.			
1	Cresheim	12	52	16	5.50	4.5	6.0	1	6	6.08	5.5	6.5	0	0	2880
2	Millard*	36	60	15	5.25	4.5	6.5	1	8	6.50	5.0	10.5	0	1	2400
3	Brightwood†	10	56	15	6.00	5.0	7.0	1	7	6.79	6.0	8.5	0	0	2150
4	Thurston ...	30	56	28	6.79	6.0	8.5	1	7	8.36	7.0	11.0	0	1	1360
5	Sparks†	34	60	18	5.45	4.5	7.0	2	20	6.68	5.5	8.5	0	0	2240
6	Cresheim* ...	20	56	19	5.82	5.0	7.5	1	11	6.82	6.0	8.5	0	0	2130
10	Lemay‡	26	60	15	4.72	4.5	5.0	1	9	5.44	4.5	6.0	0	0	4170
11	Amsden	30	60	18	6.00	5.0	8.0	2	14	6.96	5.5	9.0	0	0	2030
12	Walworth ...	30	60	17	5.71	5.0	8.0	1	7	6.29	5.5	8.5	0	0	2620
13	Thurston	24	54	19	6.57	6.0	7.0	1	7	7.79	6.0	10.0	0	0	1580
14	Moorfield	24	60	18	5.93	5.5	6.5	1	7	7.43	6.0	8.5	0	0	1750
16	Somena	20	58	16	5.50	5.0	6.0	2	14	7.07	6.0	9.0	0	0	1950
17	Wawa	30	62	18	6.39	5.5	9.5	2	18	7.77	6.0	11.5	0	2	1590
18	Nepperhan ...	24	62	18	5.79	5.0	7.0	1	7	6.00	5.5	6.5	0	0	3000
22	Thurston§ ...	6	58	26	7.21	6.0	9.5	1	7	7.79	6.5	9.5	0	0	1580
24	Colfax	16	60	16	5.92	5.0	8.0	2	12	7.42	6.0	9.5	0	0	1760
26	Onchiota	24	60	15	5.20	4.5	6.0	2	10	5.75	4.5	7.5	0	0	3430
27	Canfield	24	60	21	7.10	6.0	8.0	2	10	8.70	7.0	10.5	0	1	1280
30	Elkland	8	56	20	6.30	5.5	7.0	2	10	7.85	7.0	10.0	0	0	1560
33	Josslyn	20	62	15	5.30	5.0	5.5	2	10	6.45	6.0	8.0	0	0	2450
34	Halleck	20	62	12	5.08	4.5	6.0	1	6	6.25	5.5	6.5	0	0	2670
	21 cars			17.8	5.86	4.5	9.5	30	207	7.00	4.5	11.5	0	5	2000

*Drop-sashes of end doors open 3 inches (see Note 4).
†Drop-sash of rear door open 12 inches (see Note 4).
‡Drop-sashes of end doors open 24 inches (see Note 4).
§Train running directly with a strong wind.

7. Converting these figures into terms of air supply, as in Note 5:
Upper berth tests showing 3000 or more cu. ft. per hour, 32.84%
Upper berth tests showing 2000 or more cu. ft. per hour, 59.90%
Upper berth tests showing 1500 or more cu. ft. per hour, 83.57%
Upper berth tests showing 1000 or more cu. ft. per hour, 97.58%
Upper berth tests showing 750 or more cu. ft. per hour, 100.00%

On the basis of 207 carbon dioxid determinations in 30 upper berths of 21 steel sleeping cars equipped with exhaust ventilators, the average air supply per berth is found to be approximately 2,000 cubic feet per hour. This compares with 1,880 cubic feet for the upper berths of the older type of cars equipped with the same ventilating device, and with 1,270 cubic feet in cars ventilated by the deck-sash method.[1]

COMPARISON OF LOWER AND UPPER BERTHS IN THE SAME CAR

We are able to compare the ventilation of the lower and upper berths in all of the twenty-one cars in which upper berths were investigated. The comparison for each car is shown in Table 4.

It will be seen from this table that the ventilation of lowers and uppers is, on the average, much the same. It is relatively rare for the

TABLE 4.—COMPARISON OF THE VENTILATION OF LOWER AND UPPER BERTHS IN STEEL SLEEPING CARS EQUIPPED WITH EXHAUST VENTILATORS

Experiment	Name of Car	CO_2 per 10,000 of Air					Equivalent Hourly Air Supply per Berth	
		Aisle	Lowers		Uppers			
		Aver. CO_2	No. of Tests	Aver. CO_2	No. of Tests	Aver. CO_2	Lower	Upper
1	Cresheim	5.50	24	5.73	6	6.08	3470	2880
2	Millard*	5.25	32	6.64	8	6.50	2270	2400
3	Brightwood* ..	6.00	28	6.66	7	6.79	2250	2150
4	Thurston	6.79	21	7.12	7	8.36	1920	1360
5	Sparks†	5.45	30	6.18	20	6.68	2750	2240
6	Cresheim*	6.82	44	6.69	11	6.82	2230	2130
10	Lenay‡	4.72	18	6.06	9	5.44	2910	4170
11	Amsden	6.00	14	7.36	14	6.96	1790	2030
12	Walworth	5.71	21	7.64	7	6.29	1650	2620
13	Thurston	6.57	21	9.02	7	7.79	1200	1580
14	Moorfield	5.93	21	6.62	7	7.43	2290	1750
16	Somena	5.50	14	6.64	14	7.07	2270	1950
17	Wawa	5.39	27	7.55	18	7.77	1690	1590
18	Nepperhan	5.79	21	6.09	7	6.00	2870	3000
22	Thurston§	7.21	28	9.25	7	7.79	1140	1580
24	Colfax	5.92	24	7.01	12	7.42	1990	1760
26	Onchiota	5.20	20	5.55	10	5.75	3870	3430
27	Canfield	7.10	20	7.81	10	8.70	1570	1280
30	Elkland	6.30	20	7.01	10	7.85	1990	1560
33	Josslyn	5.30	20	5.91	10	6.45	3140	2450
34	Halleck	5.08	24	6.85	6	6.25	2110	2670
	21 cars	5.86	492	6.93	207	7.00	2050	2000

*Drop-sashes of end doors open 3 inches (see Note 4).
†Drop-sash of rear door open 12 inches (see Note 4).
‡Drop-sashes of end doors open 24 inches (see Note 4).
§Train running directly with a strong wind.

average air supply of the two to fall far apart. If one is high the other is high; if one is low the other is low. The general averages show results which would indicate that the lower receives slightly more air than the upper, but the difference is almost trifling. In thirteen cars the lower received the greater air supply; in eight cars the upper received the greater supply. This runs in part counter to the findings of the previous study,[1] where in every car the lowers were found to receive a little more air than the uppers. In that series there were only five cars in which this comparison could be made.

The simultaneous averages of CO_2 in the air of two to four lowers and in one or two uppers in the same car can be compared 148 times. The average proportion of CO_2 in the air of the lowers was less than in the uppers 83 times (56.1 per cent); it was greater 58 times (39.2 per cent.), and they were equal 7 times (4.7 per cent.).

The proportion of CO_2 in the air of the individual lower and upper berths in the same section, the samples being taken at approximately the same time, can be compared 185 times. The lower berth had less CO_2 than the upper 96 times (51.9 per cent.); it had more than the upper 62 times (33.5 per cent.), and they were equal 27 times (14.6 per cent.). The air supply is, of course, inversely as these proportions of CO_2; the lower had a greater air supply than the upper in 51.9 per cent., a less air supply than the upper in 33.5 per cent., and they were momentarily equal in 14.6 per cent. of the cases.

The upper berth has no window opening into it. The edge of the berth is about on a level with the top of the window. There is a space of about one-half inch between the edge of the berth and the wall—a total open space of about 36 square inches. Through this wide crevice the upper berth receives much of its air supply, which must then pass inward and upward across the berth and its occupant toward the ventilator exits.

GENERAL COMPARISONS

We may here bring together the comparative results for the car body and the lower and upper berths in the three classes of cars. The general averages of CO_2 and the computed air supplies are as follows:

A. Wood Cars (with Deck-Sash Construction)

1. Natural ventilation (Deck-Sash Method)
   Body of car: $CO_2 = 7.32$; air supply to car = 29,700 cu. ft. per hour.
   Lower berth: $CO_2 = 8.32$; air supply per berth = 1,390 cu. ft. per hour.
   Upper berth: $CO_2 = 8.73$; air supply per berth = 1,270 cu ft. per hour.

2. Exhaust ventilation (The Exhaust Method)
   Body of car: $CO_2 = 6.33$; air supply to car = 40,600 cu. ft. per hour.
   Lower berth: $CO_2 = 6.96$; air supply per berth = 2,030 cu. ft. per hour.
   Upper berth: $CO_2 = 7.19$; air supply per berth = 1,880 cu. ft. per hour.

B. Steel Cars (Constructed without Deck-Sashes)

Exhaust ventilation.

Body of car: $CO_2 = 5.90$;[8] air supply to car = 53,000 cu. ft. per hour.
Lower berth: $CO_2 = 6.76$; air supply per berth = 2,170 cu. ft. per hour.
Upper berth: $CO_2 = 7.00$; air supply per berth = 2,000 cu. ft. per hour.

The comparisons made in the preceding summary will be made clearer by consulting Chart 1, in which the CO_2 and the equivalent hourly air supplies per person are grouped for the three classes of cars, showing their relations as established by a study of the air of the aisle, the lower berth, and the upper berth, respectively.[9]

The preceding determinations of CO_2 and computations of air supply refer to the running car. When a train stops the active ventilation is much reduced and the CO_2 rises. It may finally reach a maximum of 20 volumes in 10,000, though it usually stops around 15. This rise in

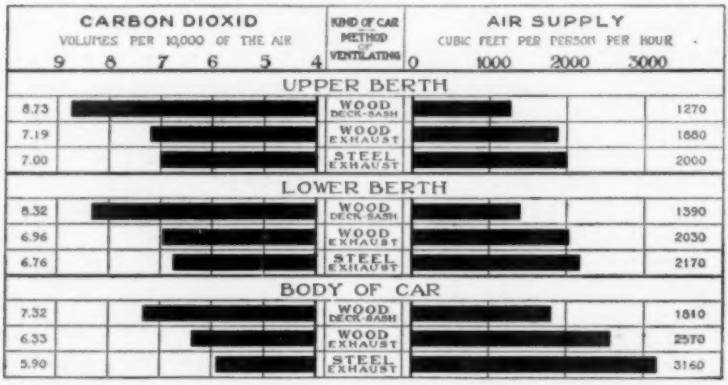

Chart 1.—Comparative CO_2 and air supply of the berths and aisle in steel cars with exhaust ventilation, and in wood cars with exhaust and natural ventilation.

the CO_2 is generally detected within a very short time — one or two minutes. On starting again the air supply is increased and the CO_2 falls rapidly. In working out the series of observations presented in this and

8. This figure applies to cars which have no opening of the drop-sash in end doors (see Note 4), as the equivalent figures in the other group apply to cars with closed doors. The windows are closed in all cases.

9. Strictly considered there is no proper comparison of the aisles as set forth in this chart, because the number of passengers varied for the different classes of cars, and as this number varies the CO_2 and the volume of air *per person* will also vary in like ratio, with any given air supply to the car. The variation in the average number of passengers for the different classes was, however, so small as to make this direct comparison allowable. In the steel cars from which the figures are drawn the average was 16.3; in the wood cars with exhaust ventilation 15.7; and in the wood cars with natural ventilation 16.4; from which it is seen that the comparison is correct to within a small fraction. This is not greater than the unavoidable error of observation.

the previous study no attention was paid to stops lasting up to four or five minutes; samples taken after those of longer duration have been dropped out of consideration. Had attention been confined strictly to the running car the results would be changed slightly; the CO_2 would be a little lower and the equivalent air supply proportionately higher.

As a general rule it is found that the CO_2 in the air of the berths and in the air of the aisle follow each other consistently in successive determinations, that of the berths averaging a little higher, as would be expected from the fact that the inflowing air from end passageways is not likely to enter them, but to be mixed in the aisles with the contaminated air that flows out from them. This consistency is well shown in Chart 2, in which Experiments 5 and 6, selected because they show the longest series of determinations, are graphically represented. The relation represented in

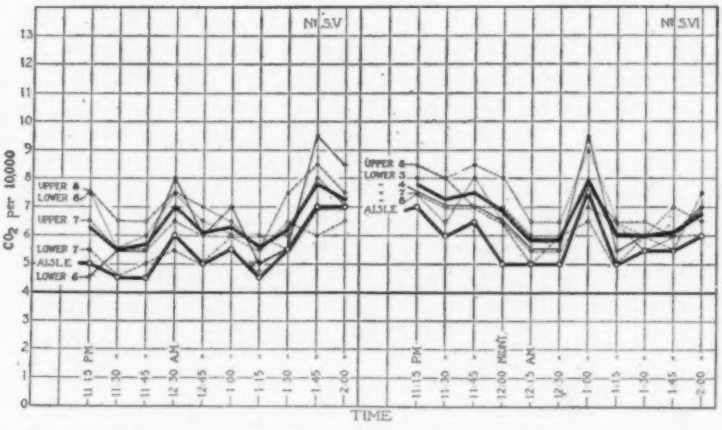

Chart 2.—Graphic representation of Experiments 5 and 6, showing consistent relation of CO_2 in aisle and berths. The lower heavy line represents the findings in the aisle, the upper heavy line the average in the berths, and the broken lines the findings in individual berths. The relation shown here is that which is usually found.

this chart is that which generally obtains, though it occasionally happens that the findings are so varied as to show little if any of such consistency. By far the most striking example of this I am able to produce is shown in Chart 3, in which Experiments 11 and 12 are represented. These two cars were on the same train and were examined at approximately the same time. Two lower berths are here represented in which the CO_2 momentarily reached 14 parts per 10,000 of air, the only instances but one in which it passed 12. It should be noted also that lower berth seven, shown at the right, shows the highest average CO_2 (10.71 per 10,000) of any berth of the whole series. It is the only one reaching an average of

10 parts per 10,000, except one berth in Experiment 22, wherein they all ran much above the general average.

From what has preceded it is seen that the air supply to the breathing zone of the steel car, constructed without deck-sashes, is materially increased over that of cars similarly equipped as to exhaust ventilating devices, but built with deck-sashes in the ordinary way. This increased ventilation is much more noticeable in the air of the aisles than in that of the berths; it results in a somewhat greater difference between the average CO_2 of the aisle and berths than was found in the previous series,

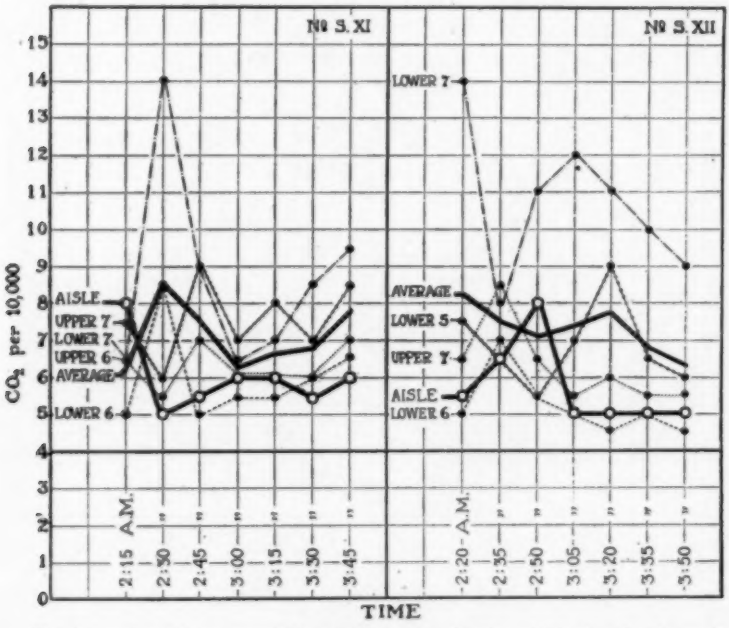

Chart 3.—Graphic representation of Experiments 11 and 12, showing inconsistent relation of CO_2 in aisle and berths. The lower heavy line connecting open circles represents the findings in the aisle, the upper heavy line the average for the berths. The lighter lines represent individual berths.

which is interpreted to mean that more air flows from the end doors and passageway windows into the body of the car by reason of there being no crevices at the top to supply the exhaust demand of the ventilators. It is probable that the power of exhaustion developed by these ventilators is very slight as measured by differences of the internal and external barometric pressure. They no doubt act mainly by furnishing a ready exit and continuous outflow of that air forced in by the wind, preventing its damming back near the places of entrance. In this way a constant

upward movement of the incoming air is assured, and this leads to a constant and equalized renewal of the air in the lower levels.

HYGIENIC CONSIDERATIONS

The principles which should govern the application of ventilating procedures, and the more important experimental evidence on which these are based, have been previously discussed.[10] It is not necessary to make further reference to the history and literature of the subject in this place.

Until very recent years our knowledge of the hygienic principles of ventilation has been exceedingly imperfect, and our opinions largely erroneous. It must be confessed that the subject is still in a rather chaotic condition; but order is beginning to come out of this chaos, if indeed it is not already fully established for those who have carefully studied the excellent experimental work of many investigators who have busied themselves to answer questions concerning why we must ventilate, what are its effects, how are these produced, and on what failures depend. Failures there have been without number, and these, too, when, according to the hygienists, the requisite quantity of pure air was introduced. It took the physiologists to answer our questions and to rid us of old and erroneous conceptions. The subject has been most clearly set forth, and much new experimental evidence has been added, in a recent communication to the Royal Society of Arts by Professor Leonard Hill,[11] of London.

On the basis of well controlled experiments, the following statements seem to be entirely warranted:

1. All trustworthy evidence goes to show that the normal expired air contains no volatile poison[12] and that it is not capable of harming the

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10. In the article referred to in Note 1, and in the Report of the Committee on the Ventilation of Cars, Transactions of the Section on Preventive Medicine and Public Health of the Am. Med. Assn., Chicago, 1911, p. 177.

11. Hill and Flack: The Influence of Ozone in Ventilation, Jour. Royal Society of Arts, London, Feb. 9, 1912, p. 344.

12. Mention should be made in this connection of the recent work of Rosenau and Amoss, "Organic Matter in the Expired Breath," Jour. Med. Research, 1911, xxv, 35. On the basis of the very delicate anaphylactic reaction they have made experiments which would seem to indicate that organic bodies belonging to the protein group may be present in the breath of healthy people, and they express the opinion that these bodies may be harmful when rebreathed.

In the air of the lungs any such volatile proteid would be constantly present in fifty or one hundred times greater concentration than in the air of occupied rooms, since the air of such rooms does not ordinarily contain more than 1 or 2 per cent. of expired air. The air which has been expelled from the alveoli and has lodged in the upper air passages during expiration, is drawn back into the alveoli during inspiration. The volume of this "dead space" amounts to about one-third of the whole volume of normal quiet inspiration; consequently, the normally inspired air is about one-third expired breath. The reinspiration of expired air

human organism when rebreathed under the ordinary conditions of ventilation.

2. The increase of carbon dioxid and the decrease of oxygen have nothing to do with the ventilation problem under normal conditions, or with the subjective or objective effects of close air. Carbon dioxid is a necessary constituent of the air of the lungs; it is not to be considered as a poison or the index of a poison. Its proportion in the air of a room is a convenient and fairly accurate index of the quantitative air supply.

3. Air performs for the body a physical function (heat-abstraction) which is quite as important as its chemical function (oxygen-supplying).

4. The ordinary defects of ventilation lie with the physical function of the air and not with the chemical.

5. Temperature, humidity and air movement are the physical qualities of the air which are of importance in this relation.

6. The success of ventilation depends on whether or not these physical qualities of the air are so regulated as to maintain its physical function of heat abstraction without embarrassment to the reflex mechanism for the regulation of body temperature. "The good effects of efficient ventilation and of out-door air depend on the coolness, the relative humidity and the motion of the air and the ceaseless variation of these qualities." (Hill.)

These six statements, then, are the main items of the code which should govern attempts to ventilate. We may not go into the practical details of their application here; but it will be noted that quantity of air as a measure of ventilation efficiency is to a large degree lost sight of, while the physical qualities of the air as they affect its ability to absorb body heat come strongly forward. The hygienic value of ventilation for the purpose of supplying chemically pure air is much less than has been generally supposed. It should now be looked on as a process to be carried out in the interest of the heat economy of the body. Metabolism is greatly influenced by the rapidity of heat dissipation, and this is controlled by external physical conditions.

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appears to be a conservative and a necessary process. It is a well known fact that the pulmonary ventilation is increased and decreased reflexly to maintain a relatively constant pressure of CO_2 (about 5 per cent. of an atmosphere) in the alveolar air. Our hypothetical poison could not become concentrated in the surrounding air unless the CO_2 also became concentated, and then the larger respiratory ventilation due to the increased CO_2 would affect the concentration of both bodies in the alveolar air in equal proportion. The increase in pulmonary ventilation which would be made necessary by the presence of 2 or 3 per cent. of expired air in that which is being breathed, in order to maintain what we must, in the nature of things, look upon as the normal dilution of the alveolar air, is very small. It amounts to no more than 3 or 4 per cent., whereas the possible increase is as many hundred per cent. Such an increase ought to lie well within our "margin of safety."

The great purpose of ventilation is the maintenance of health. This is, in general, accomplished by the maintenance of comfort, for to maintain a comfortable atmosphere is practically to maintain a healthful one. To this end the regulation of temperature and air movement are of the greatest interest and importance; as to the necessity of adding humidity to naturally dry air which has not been superheated, we really know very little. Professor Hill[11] has expressed the opinion that slight but constant changes of temperature and motion in the surrounding medium, leading to constant readjustments of the heat regulating mechanism of the body, are a very important factor in obtaining good results, and he very justly objects to the impulsion of hot air into a room as "the most objectionable of all systems of ventilation." He believes that "a cool air and radiant heat are the ideal." Cold air entering in small jets, and direct radiation, with the irregular and constantly changing convection currents, fulfill the desired conditions well.

It is on such a basis of cause and effect that cars ventilated by the method we have been considering are found to be effectively ventilated from the standpoint of air-comfort and the feeling of bodily well-being. The air supply is always adequate to prevent monotony and stagnation of the conditions surrounding the skin, yet the streams of incoming cold air are individually of such small volume, and take on such irregular and diffuse movement into the stiller body of air within, that the discomfort of draughts is almost entirely avoided. There was no report of discomfort—of so-called "stuffiness"—in the series of cars herewith presented. It will be seen by consulting the tables that their temperatures were always low. When trouble arises it is invariably connected with too much heat. When the temperature is low ventilation always seems to be good, regardless of the amount of respiratory contamination; when the temperature is high ventilation always seems to be bad, regardless of the chemical purity of the air. These are statements which have been amply verified by a long list of observations; comfort and air purity have little or no relation, but comfort and air temperature and motion are very closely related. The delicate sensory nerves of the skin have much to do with the feeling of comfort or discomfort. The judgment arrived at by means of our sensations is in the main a correct one; the air is bad or it is good, just as the sensations indicate; but it is bad or it is good in a physical and not in a chemical sense.

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A MODIFICATION OF THE TECHNIC OF THE WASSERMANN REACTION *

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The "Wassermann" blood test for syphilis is now generally recognized as a valuable aid to the clinician, not only in the diagnosis of the disease, but often as an indicator of the effect of treatment. It is not, perhaps, so generally appreciated, however, that the test, in order to be of real value, must be so carried out that a "positive" reaction will be obtained only in syphilis and in certain other conditions that are readily distinguished from syphilis. No one, thus far, has succeeded in so improving the efficiency of the test that in every case of syphilis with apparent lesions a positive reaction is obtained; so that as a diagnostic means a negative "Wassermann" reaction offers no guarantee of the absence of luetic infection; but properly performed, the test, when it results *positively*, must be expected to indicate either syphilis or certain other easily recognized conditions, such as leprosy, malaria, frambesia, paroxysmal hemoglobinuria and probably lead-poisoning.

It follows, therefore, that no modification of the original technic of the Wassermann test can be adopted if, with its use, any positive reactions are encountered in diseases other than those mentioned; and this policy would have to be adhered to even if the modifications proposed promised a great increase in the number of positive reactions obtained in known cases of syphilis.

A number of grave defects attach to the technical procedure originally recommended for the performance of Wassermann test, all of which are due to the impurities contained in the originally prescribed "antigen" preparations (i. e., the carbolized watery extract or the alcoholic extract of the liver of a syphilitic fetus). These impurities may interfere in three ways with the performance of the test: (1) by exerting a directly anticomplementary influence during the period of fixation; (2) by exerting a hemolytic influence on the blood corpuscles that are used as indicator of the reaction; and (3) by causing a pseudoreaction with the serum of individuals who are neither syphilitic nor subject to any of the other conditions that are mentioned above.

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The first two of these three disturbing actions of the impurities contained in the fetal liver extracts are avoided by selecting for test that quantity of extract which, in double amount, is neither hemolytic nor anticomplementary. The use of this quantity of extract, however, is attended with the third disturbing action and for the elimination of that source of error it has been found necessary to heat the sera to be examined for one-half hour at 50 C.[1]

One of the earliest modifications of the "Wassermann" technic was the substitution of an alcoholic extract of normal organs—for example, the heart muscle of the guinea-pig—for the extracts of syphilitic fetal liver. The most extensive studies of both syphilitic and non-syphilitic organ extracts in their "antigenic" capacity were made by Noguchi, who showed that the "antigenic" function of all the extracts resides solely in the lipoid fraction, and that the process of separating the lipoids from the extracts eliminates to a large extent the disturbing impurities.

On the basis of this important discovery Noguchi recommended the use of the isolated lipoids; i. e., the ether-soluble, acetone-insoluble fraction of an alcoholic organ extract as "antigen." Noguchi at first believed that when the isolated lipoids are used as "antigen" in the Wassermann test the sera to be examined could be used without the usual heating at 50 C.; but other workers[2] who employed the isolated lipoids found that these also, when used according to the original prescription of the Wassermann technic—i. e., as regards quantity—gave spurious positive reactions with unheated sera. For this reason, as well as on account of the practice of many workers of storing the sera for several days before examining them (during which time they often become anticomplementary), it is customary, also when the isolated lipoids are used as "antigen," to heat the sera.

Our own experiences with the isolated lipoid "antigen," which are described in detail elsewhere,[3] have convinced us that *when this "antigen" preparation is used according to the method originally prescribed for the performance of the Wassermann test, its one great advantage over the original organ extract is in part sacrificed and a new source of error is introduced.*

The sole advantage of the isolated lipoids over the original organ extracts as an "antigen" preparation lies in the availability of the "antigenic" substances in the former preparation for use in *much greater quantity* than is possible with the latter preparation. This advantage has, however, a two-fold application. We have found, in the first place, that in a considerable proportion of luetic cases—usually

1. In some laboratories higher temperatures (54 to 56 C.) are employed.
2. See article by MacRae, Eisenbrey and Swift, THE ARCH. INT. MED., 1910, vi.
3. Zeitschr. f. Immunitätsf., 1912, xiv, p. 139.

those exhibiting lesser lesions or those that have received only mercurial treatment—a positive reaction is obtained when a larger quantity of the isolated lipoids is used, but the test results negatively with smaller quantites; i. e., with quantities that represent the amount of "antigenic" substance that is used in the originally recommended procedure.

As we have just indicated, there is another way in which the availability of the isolated lipoid "antigen" for use in relatively large quantities can be applied to advantage in carrying out the Wassermann test. In determining the reacting strength of immune sera by means of the Bordet-Gengou technic—which is the prototype of the Wassermann technic—it is customary to estimate the relative values of such sera according to the smallest amount of the respective antigen with which, under like conditions, complete complement fixation is produced. Since the mechanism of the Bordet-Gengou reaction and that of the Wassermann reaction are undoubtedly identical, it must be possible to apply, in the latter test, the same principle of quantitative comparison that is used in the former.

This plan was suggested a number of years ago by Neisser, Bruck and Schucht, but in the absence of any further publication on the matter by these authors it may be assumed that their attempt in this direction was not successful.

Their failure can be easily explained.

An examination of their published protocols discloses the fact that, owing to the admixture of the usual impurities in their standard "antigen" preparation, which was an alcoholic extract of the liver of a syphilitic fetus, they were limited to the use of only eight times the smallest amount of "antigen" with which, in cases of untreated secondary syphilis, complete complement fixation could be produced. With an "antigen" preparation limited to such a narrow working range, it was not possible to apply the quantitative method of the Bordet-Gengou test.

The isolated lipoid "antigen," on the other hand, can be safely used in a quantity that is at least 500 times the minimum complete fixing unit—as determined in cases of untreated secondary syphilis—and with this preparation, therefore, the quantitative technic of the Bordet-Gengou test becomes directly applicable to the Wassermann test.[4]

If then, as is commonly done, the isolated lipoid "antigen" is employed for the Wassermann test in only one quantity—i. e., one-half of the largest amount that, by itself, is neither hemolytic nor anti-

4. It must be emphasized here that whether the reacting strength of luetic sera as determined according to the minimum fixing quantity of "antigen" does or does not always coincide with the degree of severity of the syphilitic process that exists at the time of the examination, the result of such a determination does give a true index of the concentration of the reacting substances in the sera.

complementary—the advantage of the quantitative method of the Bordet-Gengou test is sacrificed.

But the sacrifice of the quantitative technic is not the only objection that must be urged against the application of the Wassermann prescription to the use of the isolated lipoid "antigen." We have mentioned the experience of MacRae, Eisenbrey and Swift, who found that even with the isolated lipoid "antigen," unless the sera to be examined are heated, "positive" reactions are sometimes obtained in many diseases other than syphilis.[5]

The practice of those who use the isolated lipoid "antigen" of heating the sera to be examined in order to avoid such spurious positive reactions, greatly exaggerates a new source of error—one that is not encountered when the smaller quantities of the "antigenic" substances are used, as under the original Wassermann technic—which attaches to the use of the isolated lipoid "antigen." The source of error referred to is the familiar prezone phenomenon of wanting reaction, which occurs in the testing of specific antisera when either of the two reacting substances, antigen and antibody, is combined with the other in a quantity that is in excess of a definite proportion.

The prezone phenomenon that is sometimes produced in the performance of the Wassermann test is due to the use of a relative excess of the "antigenic" substances. It is much more frequently met with when the sera to be examined are heated, but it has been observed by us in twelve instances in which the sera had not been heated.

The source of error presented by the prezone phenomenon occurring in the Wassermann test can be easily eliminated by carrying out each test with descending quantities of the "antigen," so that it is not necessary, only on account of this possible fallacy, to omit the heating of the sera. That the custom of heating the sera should be discarded when it is possible is, however, evident in view of the well-known fact that heating considerably reduces the reacting power of luetic sera.

As a matter of fact, the heating of the sera *can* be dispensed with, for we have found an equally certain and much simpler way to accomplish the end for which the heating was usually performed, namely, to avoid the spurious "positive" reactions of diseases other than syphilis. We have observed, in a series of several hundred examinations, that whereas with unheated sera 0.2 c.c. of a 1 to 10 dilution of our 2 per cent. lipoid solution often gives complete fixation in many conditions other than syphilis, no such spurious reaction is produced by 0.1 c.c. of that dilution of the lipoids. With one exception all of the fixations produced with the latter

5. Notwithstanding this serious complication these writers conclude that "the Noguchi method, using *active* serum, gives the most sensitive reaction in syphilis." We have already pointed out the fallacy of this view.

quantity of the isolated lipoid "antigen" have been obtained in cases of known syphilis. That one exception was in a case of paroxysmal hemoglobinuria, in which disease the original Wassermann technic produces regularly a "positive" result."

Instead of heating the sera, therefore, we avoid the spurious or "pseudoreactions" by using about half the prescribed amount of the isolated lipoid "antigen," which, as we have already stated, is 500 times the minimum fixing quantity for secondary syphilis.

SUMMARY

The substance of the preceding discussion may be more briefly presented as follows:

1. Only the lipoid fraction of organ extracts possesses the "antigenic" properties requisite for the performance of the Wassermann blood test for syphilis (Noguchi).

2. On account of the large admixture in the originally recommended "antigen" preparations (i. e., the carbolized watery extract and the simple alcoholic extract of the liver of a syphilitic fetus) of substances not possessing "antigenic" properties, the quantitative limits within which the "antigenic" substances are available for the Wassermann test, are very narrow—4 to 8 units. When such extracts are used for the test the sera must be heated, otherwise positive reactions are obtained in many diseases besides syphilis. The reacting strength of luetic sera is considerably reduced by heating.

3. The quantitative limits within which the isolated lipoid "antigen" is available for the Wassermann test, are relatively wide—at least 500 units—so that with this preparation positive reactions can be obtained with luetic sera with which the test would result negatively if only the relatively small amount of "antigen" available under the original Wassermann procedure was used; furthermore, on account of the greatly extended working-range of the isolated lipoid "antigen" preparation the usual quantitative method of determining the reacting strength of specific antisera according to Bordet-Gengou can be employed.

4. When the isolated lipoid "antigen" preparation is used according to the original Wassermann prescription, "positive" reactions are often obtained with active sera in many diseases other than syphilis. These spurious or "pseudoreactions" can be entirely avoided, without heating the sera, by not using more than about half of the prescribed amount of the "antigen" preparation; i. e., one-fourth instead of one-half of the largest quantity of the preparation that by itself is neither hemolytic nor anticomplementary.

5. When the isolated lipoid "antigen" preparation is used in descending quantities in the Wassermann test, the prezone phenomenon is some-

times observed, which is due to the use of an excess of the "antigenic" substances. This source of error is met with in a considerable proportion of heated luetic sera, and occasionally even when the sera are not heated; it can be avoided only by the use, in each test, of descending quantities of the "antigen" preparation.

PROPOSED TECHNIC

Antigen.—The most convenient source of suitable lipoids is the heart muscle of the ox. The muscular tissue is dissected out from the heart of a recently slaughtered ox, and, after being finely comminuted in a meat grinder, is shaken well with about ten volumes of 95 per cent. alcohol. The alcoholic extract is filtered after five to ten days and evaporated nearly to dryness with the use of an electric fan. The sticky residue is extracted with ordinary ether and the ether extract again evaporated with the use of the fan, supplemented finally with gentle warming. The resulting residue is then extracted with water-free ether in small quantity and the clear solution obtained by centrifugation is mixed with five volumes of acetone. After thorough shaking the fluid is poured off the waxy precipitate, which is then shaken several times with fresh portions of acetone. The stock solution is a filtered 2 per cent. solution of the lipoids in pure methyl alcohol. For each series of tests a fresh emulsion is made by diluting one part, by volume, of the stock solution up to ten parts with physiological salt solution (Ringer's). Of this 0.2 per cent. emulsion, 0.4 c.c. has never produced the slightest hemolysis when mixed with 0.1 c.c. of a 5 per cent. suspension of sheep's blood, nor is that amount anticomplementary with 0.01 c.c. of guinea-pig's serum (indicator 0.1 c.c. of 5 per cent. sensitized sheep's blood).

Some lipoid preparations from ox's heart muscle are not capable of functionating as "antigen" in the Wassermann test. Of four such preparations made from four different ox-hearts, one was completely lacking in "antigenic" property. The other three were efficient, and equally so, in that capacity. The "antigenic" property of our first preparation has remained unchanged for more than one year.

In the interest of economy of materials, all the reagents entering into the Wassermann test may be used in one-tenth of the usual quantities. Under this condition we have found that with cases of untreated secondary syphilis, the minimum fixing amount of ox-heart lipoids is frequently as little as 0.0002 c.c. of a 0.2 per cent. emulsion, that is, 0.0000001 g.

Some of the sera that have been obtained more than twenty-four hours previous to the examination are found to have become anticomplementary, that is, 0.4 c.c. or less, of the diluted serum inhibits by itself the complementary function of 0.1 c.c. of guinea-pig's diluted serum.

In order to remove this anticomplementary property it is necessary to heat such sera for one-half hour at about 50 C. For the exact determination of the fixing strength of a luetic serum, it is, therefore, important that the test be made within twenty-four hours after the blood has been taken, so that the necessity of inactivation may be avoided. If, as we have always done, the reagents entering into the Wassermann test are all used in one-tenth of the usual quantities, the amount of the patient's serum required for such examination is correspondingly reduced; so that sufficient blood for the test can be easily obtained from the ear or finger. Such small amounts (2 c.c.) are best defibrinated and centrifugated at once. The serum can then be removed with a pipet and is ready for immediate examination.

Complement.—This function is supplied by 0.1 c.c. of a 1 to 10 dilution of fresh guinea-pig's serum in physiological salt solution. Whenever this serum is naturally hemolytic for sheep's blood corpuscles, the natural hemolysin is to be removed by the cold separation method—one to two hours at 0 C. in contact with washed sheep's corpuscles.

Indicator.—Two per cent. sheep's blood corpuscles sensitized with two to three minimum hemolytic doses of immunized rabbit's serum are used as indicator. To each tube is added 0.25 c.c. of this suspension, representing 0.1 c.c. of the usual 5 per cent. suspension.

When the test was carried out according to the plan that we have described, we were not able to observe any essential difference in the results that could be due to differences, within the limits given above, in the degree of sensitization of the blood corpuscles that were used as indicator of the reaction. The sensitization should be so adjusted to the complementary activity of the guinea-pig's serum that not more than 0.025 c.c. of that serum diluted 1 to 10 will be required, and that not less than 0.0125 c.c. will be able completely to hemolyze 1 unit (0.25 c.c. of a 2 per cent. suspension) of the sensitized blood cells.

In the practical performance and reading of the Wassermann test we proceed as follows:

1. All the reagents entering into the reaction of fixation can be most conveniently diluted 1 to 10 with physiological salt solution. The sensitized sheep's blood suspension may be 2 per cent. (unit=0.25 c.c.) or 5 per cent. (unit=0.1 c.c.).

2. Five different amounts of a 0.2 per cent. emulsion of ox-heart lipoids are to be combined with 0.2 c.c. of the patient's diluted serum and 0.1 c.c. of the diluted guinea-pig's serum. The five amounts of antigen are 0.1, 0.05, 0.02, 0.01 and 0.001. A series of examinations with non-luetic sera should be made for the purpose of determining the lower limit of pseudo-reaction.

3. If complete fixation of complement occurs with all of the five quantities of "antigen" or with only the smallest two or three quantities, we report a "strongly positive" reaction; if with 0.001 c.c. hemolysis has not been prevented, but fixation has occurred with all the other combinations or with the lesser one or two quantities of "antigen," we report a "positive" reaction; if hemolysis is not prevented with 0.001 nor with 0.01 c.c., but fixation occurs with any of the other amounts of the "antigen," we report a "weakly positive" reaction.

We have never met with an occasion for reporting a "doubtful" reaction.

We have confirmed the observations of Jacobsthal and of Guggenheimer, that with some luetic sera a positive Wassermann reaction can be obtained when the "incubation" for fixation is carried out at ice-box temperature, whereas the test as usually performed results negatively. The reverse of this, also, has been found, in some instances, to be true.

In view of these facts it is necessary to perform each test in duplicate series, one for fixation at ice-box temperature, and the other for fixation at 37 C. The period of incubation for fixation at low temperature may be twelve to eighteen hours (conveniently over night).

In the table are given examples of the results that we have obtained with our technic, together with our "reading" of them.

TABLE GIVING EXAMPLES OF THE RESULTS OF THE WASSERMANN REACTION OBTAINED UNDER AUTHORS' TECHNIC, CLASSIFIED ACCORDING TO REACTING STRENGTH OF THE SERA

Indicator 0.25 c.c. of 2 per cent sheep's corpuscles. In each tube 0.02 c.c. of patient's serum + 0.01 c.c. of guinea-pig's serum.

————0.2 per cent. Emulsion of Ox-Heart Lipoids————					
0.1 c.c.	0.05 c.c.	0.02 c.c.	0.01 c.c.	0.001 c.c.	
0	0	0	0	0	Strongly positive reactions.
++++	++	0	0	0	
++++	++++	++	0	0	
0	0	0	0	++++	Positive reactions
++++	++	0	0	++++	
++++	++++	++	0	++++	
0	0	0	+++	++++	Weakly positive reactions.
0	0	+	++++	++++	
0	++	++++	++++	++++	
++++	0	0	++	++++	
++++	+++	+	+	++++	

++++ = complete hemolysis; +++ = very strong hemolysis; ++ = partial hemolysis; + = slight hemolysis.

STUDY OF THE CHEMISTRY OF RENAL CALCULI*

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Rowlands,[1] in his examination of twenty-two stones, came to the following conclusions: that renal calculi are composed almost entirely of calcium oxalate; that uric acid is almost always absent, or present in very small traces; that phosphates are commonly present.

Mackarell, Moore and Thomas,[2] following the investigations of Rowlands, concluded that these results have a marked bearing on the calcium metabolism in gout and allied conditions. They examined twenty-four renal stones and they corroborated the findings of Rowlands. They recommended that when a calculus has been obtained by operation or otherwise, it should be analyzed, and if it is found to be composed of calcium salts, the patient should be put on a course of *acid* treatment and not alkaline medications, as has been the custom.

I have examined a series of sixteen stones from patients of the Mount Sinai and various other hospitals in New York City. The patients were immigrants to the United States from all parts of Europe, most of them from Russia and Austria. From the histories of these patients, no evidence of gout or a gouty diathesis could be obtained. They were all of the poorer class, living in the crowded tenement districts of New York, and not at all addicted to high living, or to the use of wines and ales.

The results of Rowlands and Moore are quite startling. Every textbook states that calculi of uric acid, or of the salts of uric acid, are by far the most frequent. Osler, Wood, Hammarsten, Halliburton, Wells, Allbutt, etc., invariably introduce their remarks on the chemistry of renal stones by some statement that the urates are the most frequent components. The quantitative examinations that have been made up to now would impress one with the certainty that the chemistry of the nephroliths was an established fact, and indeed, when I first read the article of Rowlands and the one by Mackarell, Moore and Thomas, I doubted the general application of their findings.

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1. Rowlands, J. S.: Biochem. Jour., 1908, iii, 346.

2. Mackarell, W. W.: Moore, B., and Thomas, W. T.: Biochem. Jour., 1910, v, 161.

It is interesting to note the results of previous examinations. Brande,[3] in a series of 150 cases, found that sixteen calculi were composed wholly of uric acid, while the rest contained some. Fourcroy and Vauquelin[4] found lithic acid in the greater number of 500 stones. Pearson[5] found this acid in the majority of 300 concretions. Henry states that of 187 stones, 158 had uric acid nuclei. Of 545 cases of stone, Ultzman[6] found that 80.9 per cent. contained a nucleus of uric acid, while 5.6 per cent. were composed of calcium oxalate. Recently chemical analyses have been made by Morris, Israel and Johnson[7] with the unvarying conclusion that urates predominate in their composition.

Young,[8] in Osler's Modern Medicine, says: "Such methods of quantitative chemical analysis of calculi as have been used until quite recent years were so inexact that they sometimes furnished misleading information." He continues to say, "The physical characteristics of calculi vary greatly and are somewhat indicative of their composition. On these rather than on chemical analysis, have been based many statements as to the nature of renal calculi."

In the series of sixteen cases that I have analyzed, no conclusions could be drawn from the appearance and consistency of the stones as to their chemical composition. Some, that were quite soft and easily pulverizable, were almost wholly composed of calcium oxalate. Others, that were white and irregular and of excessive hardness contained a high percentage of uric acid. The characteristic "mulberry stones," "stag-horn," or coral calculus, and "jack-stone" calculus did not appear in this series.

As Rowlands suggested, the rate and process of formation of the stone have more to do with the hardness or softness of the calculus than its chemical composition.

METHODS OF ANALYSIS

The methods of analysis followed were almost identical with the one suggested by Mackarell, Moore and Thomas.

a. Physical Characteristics: The size, shape, color, and consistency of the stones were noted. The method used to determine the hardness or softness of the stone was by simple crushing, noticing the force exerted in breaking up the stone.

b. The murexid test for uric acid was performed on each stone, and positive results were obtained in all cases.

c. Chemical Composition: The stone after being finely pulverized, was carefully weighed in a drying flask (whose weight was previously found), and then dried in an oven for about two hours at a temperature of 100 to 105 C., and again weighed, the loss in weight being taken as moisture.

3. Brande: Hooper's Med. Dic., 1820.
4. Fourcroy and Vauquelin: Ann. d. chem., 1805, lvi, 258.
5. Pearson: Tr. Roy. Philosoph. Soc., 1798, xv, 59.
6. Ultzman: Cited after Hammarsten's Physiol. Chem., 1908.
7. Johnson: New York Med. Jour., 1905, lxxxvii, 209.
8. Young: Osler's Modern Medicine, 1908, vi, 316.

Quantitative Determination of Uric Acid.—A quantity varying according to the amount of the stone available, was taken and accurately weighed. This was then placed in a porcelain dish, treated with hydrochloric acid (1.4) and heated on a steam bath until as much as possible had been dissolved. It was then filtered through a weighed Gooch filter, the residue well washed, and then dried at 100 C. for from one to two hours until the weight was constant; this weight was recorded. The residue in the Gooch, asbestos and all, was next treated with strong sulphuric acid. The acid was then diluted and titrated with n/20 potassium permanganate solution, 1 c.c. of which is equal to 0.0075 gm. of uric acid. A control was always performed with the sulphuric acid and water in order to get an accurate result, the amount of permanganate taken by the control being deducted from the result of the former titration.

Quantitative Determination of Calcium Oxalate.—The filtrate obtained after digesting the stone with hydrochloric acid was next mixed with the washings of the residue, and ammonium chlorid and ammonium hydroxid added in excess. The precipitate obtained was filtered and thoroughly washed until free from chlorids (the washings being tested with silver nitrate). The filtrate and the washings were boiled and ammonium oxalate added until precipitation was complete. The precipitate was allowed to stand twenty-four hours until it had completely settled. The liquid was filtered off, and the precipitate washed by decantation until free from chlorids, which would otherwise interfere with the permanganate titration. The precipitate was washed from the filter paper into a beaker, first by means of hot water and then with 10 per cent. sulphuric acid and finally all the acid was washed into the flask by means of hot water. The whole was then mixed, cooled and made up to 1,000 c.c. Of this 50 c.c. were pipetted off, and titrated at a temperature of 65 C. with n/20 potassium permanganate solution, 1 c.c. of which is equivalent to 0.0019 gm. of calcium, or 0.00608 gm. of calcium oxalate.

Quantitative Estimation of Total Nitrogen.—Another portion of the stone was then weighed out, and placed in a Kjeldahl flask, and the total nitrogen determined by the Kjeldahl process.

Quantitative Estimation of Phosphates.—Phosphates were estimated as phosphorus pentoxid by the following method: A portion of the powdered stone having been weighed, was put into a Kjeldahl flask and 20 c.c. of a mixture of equal parts of concentrated sulphuric acid and concentrated nitric acid were added. The Kjeldahl flask and contents were then heated until colorless. This usually took thirty-five minutes. Five drops of fuming nitric acid were then added and it was again heated until colorless. The contents of the Kjeldahl flask were cooled and then diluted with water. It was next neutralized with ammonium hydroxid and then reacidified with concentrated nitric acid. The mixture was then put into a beaker and to this were added 50 c.c. of a 60 per cent. solution of ammonium nitrate, and 25 c.c. of a 10 per cent. solution of ammonium molybdate. This was allowed to stand 12 to 24 hours at 60 C. and was then filtered. The precipitate was dissolved in ammonium hydroxid, and 10 c.c. of concentrated hydrochloric acid were added. To this were added 25 c.c. of magnesia mixture. After standing fifteen minutes an excess of ammonium hydroxid was poured in and the mixture allowed to stand for twenty-four hours. The precipitate was filtered on a weighed Gooch filter, burnt, and from the weight of the pyrophosphate of magnesium the weight of phosphorus pentoxid was estimated.

Most of the stones examined were mainly composed of calcium oxalate. The percentage of calcium oxalate varied from 29.5 per cent. to 94.7 per cent. The physical appearance and the consistency of the stone were not at all indicative of its chemical constituents. The one which was 94.7 per cent. oxalate was a ureteral stone, brown in color, very irregular in shape, very soft and brittle. The stone which contained 29.5 per cent. oxalate was very hard, dark brown in color, spheroidal, with many

irregular projections—the only stone that could be called "mulberry"-like —and it contained 7.46 per cent. uric acid and 56.2 per cent. phosphorus pentoxid.

All the stones gave the murexid test, so that either uric acid or its salts were present in each case. The statement made by Rowlands, and later by Mackarell, Moore and Thomas, that uric acid is usually absent in urinary calculi must, therefore, be modified. Though it is present ordinarily in very small amount, still its presence must be recognized. The amount of uric acid found, ranged from 40.6 per cent. to 0.2 per cent. Nevertheless, the amount of uric acid usually present is negligible as compared with the calcium oxalate. The urate stone, so graphically depicted in the text-books, is a very rare occurrence in the quantitative laboratory. The total nitrogen determination, when calculated as uric acid, rarely exceeded the amount of this acid estimated according to the method used by Moore.

Phosphates were found in nearly all the calculi, and in some stones the percentage of the phosphates was very high. No carbonates were found. This quite agrees with Rowlands, who found phosphates in traces in nearly all the stones and carbonate in only two out of a series of twenty-two examinations.

One of the conclusions that Mackarell, Moore and Thomas draw from the fact that they did not find uric acid in renal calculi is, that gout may be a disease due to deficient calcium metabolism, and that it is rather this deficiency than the disturbance in the uric acid output that has to be treated. This assumption is not warranted. Renal calculus is not always, nor even usually, due to gout. The fact that gouty patients sometimes suffer from gravel cannot be brought forward as an argument that whatever is the metabolic derangement in lithiasis is also the causative factor of podagra. Sir William Roberts[9] states that the impression that gouty individuals invariably suffer from calculus disease and the impression that patients who suffer from nephrolithiasis are also afflicted with gout, are erroneous. In certain portions of India, gravel in the urine and stone in the kidney are very common complaints and still gout, or the gouty diathesis, is unknown. In Norfolk[10] calculus disease is very common, while podagra is rare. The reverse is the case in other portions of England. As Fagge[11] asserts, there are certain districts where travelers (not at all gouty) acquire lithiasis, and are cured only on removal from the territory.

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9. Roberts: Allbutt's System of Medicine.
10. Yalloly: Tr. Roy. Philosoph. Soc., 1839, lxxxix, 149.
11. Fagge: Cited from Osler's Modern Medicine.

DETAILS OF ANALYSES OF THE SIXTEEN CALCULI

The subjoined tables record the results obtained. A brief summary of the history of each patient (when a history could be obtained) and a macroscopic description of each calculus are also given.

CALCULUS 1.—*Gross Appearance.*—The stone was in two portions. Each one was irregularly semilunar, very hard, white and smooth. The stone weighed 12.0446 gm.

Chemical Examination.—In 0.942 gm. of the powdered stone there were 0.3532 gm. calcium oxalate or 37.4 per cent. and 0.034 gm. uric acid or 3.59 per cent. It contained 51.59 per cent. phosphorus pentoxid—0.7569 gm. of the stone gave 0.3898 gm. of phosphorus pentoxid.

CALCULUS 2.—*History.*—Patient C. I. of Mount Sinai Hospital. Stone given to me by Dr. Morris H. Kahn. Ureteral stone. Patient had characteristic renal colics and was operated on by Dr. Brettauer. She is Russian by birth.

Gross Appearance.—Small, irregular stone, very brittle and soft, brown in color.

Chemical Examination.—The stone weighed 0.5114 gm., of which 0.0210 was moisture, so that the dried stone weighed 0.4904 gm. The moisture was 4.1 per cent. From 0.1399 gm. of the stone, 0.13254 gm. calcium oxalate was obtained or 94.7 per cent., and 0.003075 gm. uric acid or 2.1 per cent. The yield of phosphorus pentoxid from 0.1174 gm. was 0.0061 gm. or 5.3 per cent.

CALCULUS 3.—*History.*—Stone was given to me by Dr. M. H. Kahn. Patient was in the Mount Sinai Hospital. Suffered from an attack of pain and hematuria. No history of gout. Stone was removed by nephrotomy.

Gross Appearance.—A very hard stone with spinous processes. It was dark brown in color and irregularly spheroidal.

Chemical Examination.—The stone weighed 13.982 gm., and when dry it weighed 13.6805 gm., the moisture being 2.1 per cent. The yield of calcium oxalate from 1.015 gm. was 0.2988 gm. or 29.5 per cent. From the same stone portion 0.07575 gm. uric acid, or 7.46 per cent., were obtained. The phosphates were in excess; 1.3971 gm. of the stone gave 0.78212 gm. phosphorus pentoxid, or 56.2 per cent.

CALCULUS 4.—Clinical history unknown. Patient, L. M.; Jewish; of the poorer class; immigrant to the United States. Stone given to me by Dr. M. H. Kahn.

Gross Appearance.—The stone was triangular in shape, smooth, hard, grayish in color, and regular in form.

Chemical Examination.—The stone weighed when dry 0.5940 gm., having lost weight in drying, 0.0069 gm. The moisture was therefore 1.08 per cent. In 0.2340 gm. of the stone there were found 63.4 per cent. calcium oxalate and 40.06 per cent. uric acid. In 0.1256 gm. of the stone 7.3 per cent. phosphorus pentoxid was found.

CALCULUS 5.—*History.*—Patient, A. S., male, of Mount Sinai Hospital. Long history of pain, hematuria, pyuria, and finally sepsis. Nephrectomy performed on the patient for renal calculus. Stone given to me by Dr. M. H. Kahn.

Gross Appearance.—The stone was broken into several pieces. It was smooth and irregularly faceted, and whitish yellow in color. Its consistency was very hard.

Chemical Examination.—The stone weighed, when dry, 14.9483 gm., having lost 0.0477 gm. as moisture, or 0.23 per cent. The stone was almost wholly composed of calcium oxalate—94.1 per cent. Uric acid was 0.2 per cent. and phosphorus pentoxid was 6.1 per cent.

CALCULUS 6.—*History.*—This stone was from the other kidney of the same patient, A. S. (Case 5). A nephrotomy was performed for this stone.

Gross Appearance.—The stone was quite small, smooth and firm and yellowish-white in color.

Chemical Examination.—The stone weighed 2.4505 gm. Moisture was 3.2 per cent. It is interesting to note that this stone, removed from the same patient as Calculus 5, contained 72.3 per cent. calcium oxalate and 23.6 per cent. uric acid. This is a remarkable fact, if a diathetic derangement is to be taken as the etiological factor of renal stones. Phosphorus pentoxid was present to the extent of 4.3 per cent.

CALCULUS 7.—No history of the patient.

Gross Appearance.—The stone was smooth, round and hard. It was flat and yellow.

Chemical Examination.—The stone weighed, when dry, 6.0971 gm. Moisture was 1.3 per cent. In 0.4163 gm. of the stone, there were 0.385 gm. of calcium oxalate or 90.5 per cent. and 0.0374 gm. uric acid or 9.01 per cent. Phosphorus pentoxid gave a yield of 0.5 per cent.

CALCULUS 8.—No history of the patient.

Gross Appearance.—Smooth, white, hard stone.

Chemical Examination.—The stone weighed 4.0349 gm. Its moisture was 0.04 per cent. In 0.5914 gm. of the stone, there were found 91.7 per cent. calcium oxalate, and 1.01 per cent. uric acid. Phosphorus pentoxid was found to be 6.4 per cent.

CALCULUS 9.—Stone given to me by Dr. J. Rosenbloom. No history of the patient.

Gross Appearance.—The stone was very hard and very irregular. It was yellowish-white in color.

Chemical Examination.—The stone weighed 5.7725 gm. and the moisture was 0.1324 gm. or 0.02 per cent. From 0.9133 gm. of the stone were obtained 0.86023 gm. of calcium oxalate or 94.2 per cent. and 0.0164 gm. uric acid or 1.8 per cent. The yield of phosphorus pentoxid was 0.01281 gm. from 0.2784 gm. of the stone, or 4.6 per cent.

CALCULUS 10.—Patient S. S. of Mount Sinai Hospital. Stone given to me by Dr. M. H. Kahn.

Gross Appearance.—A large white stone. It was very hard so that pounding had to be exerted in order to crush it. It was very rough and very irregular. It was composed of three pieces.

Chemical Examination.—The stone weighed 15.9125 gm. In 0.3136 gm. of the stone, there were found 0.2314 gm. of calcium oxalate, or 73.8 per cent. and 0.0235 gm. uric acid or 7.5 per cent. The yield of phosphorus pentoxid was 20.1 per cent., i. e., 0.4182 gm. of the stone gave 0.08405 gm. of the pentoxid.

CALCULUS 11.—*History.*—No history of patient.

Gross Appearance.—Large white stone; very hard, so that much pounding had to be exerted in order to crush it. It was very rough and very irregular. It was composed of three pieces.

Chemical Examination.—The stone weighed 15.9125 gm. In 0.3136 gm. of the stone, there were found 0.2314 gm. of calcium oxalate, or 73.8 per cent., and 0.0235 gm. uric acid, or 7.5 per cent. The yield of phosphorus pentoxid was 20.1 per cent., i. e., 0.4182 gm. gave 0.08405 gm. of the pentoxid.

CALCULUS 12.—*History.*—Patient was in the Mount Sinai Hospital. Was an immigrant to New York. History of renal calculus symptoms. Stone given to me by Dr. M. H. Kahn.

Gross Appearance.—The stone was brown, light, soft, smooth, and regular and oval in shape.

Chemical Examination.—The stone weighed 0.9329 gm. Moisture was 0.0041 gm. In 0.2179 gm. of the stone there were found 0.17519 gm. calcium oxalate—

80.4 per cent.—and 0.0224 gm. of uric acid or 10.3 per cent. In 0.1745 gm. of the stone there were 0.01137 gm. of phosphorus pentoxid or 6.5 per cent.

CALCULUS 13.—*History.*—A ureteral stone, given to me by Dr. M. H. Kahn. It was removed by nephrotomy.

Gross Appearance.—The stone was in three small portions. It was a very smooth, dark, round calculus, of excessive hardness.

Chemical Examination.—The stone weighed 0.1612 gm. of which there were 91.3 per cent. calcium oxalate, 2.46 per cent. uric acid, and 5.23 per cent. phosphorus pentoxid.

CALCULUS 14.—No history of the patient. The stone was given to me by Dr. M. H. Kahn.

Gross Appearance.—The whole stone was rounded, irregular, with spinous projections of the size of a walnut. The portion examined was as white as chalk, brittle in general, though firm in areas, and very irregular.

Chemical Examination.—The whole stone was not weighed. The portion analyzed weighed 1.6064 gm. of which 0.0016 gm. was moisture. From 0.2467 gm. of the powdered stone, there were obtained 0.17318 gm. calcium oxalate, or 70.2 per cent., and 0.0298 gm. uric acid or 12.1 per cent. Phosphorus pentoxid was present to the extent of 16.9 per cent.

CALCULUS 15.—*History.*—Renal stone removed *post mortem* from kidney by Dr. J. Rosenbloom. No clinical history of patient.

Gross Appearance.—The calculus was very dark brown, broken in several places and shaped like the pelvis of the kidney. It was very hard and very jagged.

Chemical Examination.—The stone weighed 12.3471 gm., of which there was 0.3 per cent. moisture. The portions examined gave a yield of 90.37 per cent. calcium oxalate, 3.4 per uric acid, and 6.21 per cent. phosphorus pentoxid.

CALCULUS 16.—No history of the patient. Stone given to me by Dr. Rosenbloom.

Gross Appearance.—Grayish-white brittle stone, rounded, with some projections. It crumbled very easily on the slightest pressure.

Chemical Examination.—The stone weighed 9.7621 gm. Its moisture was 3.1 per cent. The yield of calcium oxalate from 0.2317 gm. of the stone was 0.2114 gm., or 91.3 per cent. The yield of uric acid from the same stone portion was 0.0156 gm. or 7.2 per cent. The phosphorus pentoxid was 2.1 per cent.

TABLE OF PERCENTAGE COMPOSITION OF THE CALCULI

Number	Weight	Moisture, Per cent.	Ca Oxalate, Per cent.	Phosphorus Pentoxid, Per cent.	Uric Acid, Per cent.	Total Nitrogen, Per cent.
I	12.0446	6.11	37.4	51.59	3.59	0.91
II	0.5114	4.1	94.7	5.3	2.1	1.2
III	13.982	2.1	29.5	56.2	7.46	4.2
IV	0.6009	1.08	63.4	7.0	40.06	27.3
V	14.998	0.23	94.1	6.1	0.2	1.3
VI	2.4505	3.2	72.3	4.3	23.6	12.9
VII	6.175	1.3	90.5	9.01	0.5	4.21
VIII	4.0349	0.04	91.7	6.4	1.01	0.76
IX	5.7725	0.02	94.2	4.6	1.8	1.02
X	2.8304	0.15	81.6	9.5	9.3	3.72
XI	15.9125	0.4	73.8	20.1	7.5	3.1
XII	0.9329	0.43	80.4	6.5	10.3	4.62
XIII	0.1612	0.05	91.3	5.23	2.46	1.09
XIV	1.6064	0.099	70.2	16.9	12.1	4.3
XV	12.3471	0.3	90.37	6.21	3.4	2.58
XVI	9.7621	3.1	91.3	2.1	7.2	5.81

In the paper by Mackarell, Moore and Thomas, the authors suggest that gouty tophi may be composed almost entirely of calcium oxalate, in spite of the prevailing idea that they are composed of the salts of uric acid. They had no material on hand and their suggestion was purely hypothetical. I have been able to investigate the composition of three tophi—two from the lobules of the ear and one from a gouty concretion in a joint. The concretions, however, were in such small amounts that no quantitative examination could be made. I, therefore, did only the murexid test, *and it gave a negative result in each of the three cases.* H. Matthes and E. Ackerman[12] lately examined a very large gouty deposit and found that it contained 46.7 per cent. moisture and 41.7 per cent. dry substance, of which there was 76.72 per cent. sodium urate. This examination would quite agree with the findings of Wollaston, who was the first to state that gouty tophi are mainly composed of sodium and ammonium biurate, instead of calcium carbonate as was generally believed in his day.

CONCLUSIONS

1. The large majority of renal stones are composed of the oxalate of lime; sometimes the calcium salt is the only component of the stone.

2. Uric acid and the urates are found in small quantities in all renal calculi, but it is rare to find a nephric stone composed mainly of uric acid or the urates.

3. The shape, color, consistency, etc., of a stone do not constitute criteria of its chemical composition.

4. Gouty tophi are not always composed of uric acid or the urates. In three concretions examined, a negative murexid test was invariably obtained.

These investigations were conducted in the laboratories of Prof. William J. Gies, to whom I beg to express my sincere thanks for his kind aid and suggestions throughout the undertaking. I am greatly indebted to Dr. Jacob Rosenbloom and Dr. Morris H. Kahn for their kind cooperation in procuring material for the chemical examinations.

437 West Fifty-Ninth Street.

12. Matthes, H., and Ackerman, E.: Chemisches Zentralbl., 1909, lxxx, 1496.

CAUSES OF VARIATION IN THE PLATELET COUNT *

EXPERIMENTAL RESULTS SHOWING THE EFFECT OF DIPHTHERIA TOXIN, BENZOL AND TUBERCULIN ON THE PLATELET COUNT IN RABBITS

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Prior to the introduction of the Wright and Kinnicutt method,[1] the technic for counting blood-platelets was either so laborious or so inexact that very little interest was taken in the subject by clinicians, and very few results were reported. The results reported have been at variance. Investigators have not agreed on the platelet count in health, nor on the changes which occur as a result of disease. The divergent opinions regarding the normal count are due evidently not only to the use of different counting methods, but also to a lack of unity regarding the identity of platelets. Differences of opinion respecting the pathologic changes in the count are largely due, as I shall endeavor to point out, to the fact that the count may be enormously increased or decreased by the action of the same agents. It would appear that in some diseases very high and very low counts have the same cause and almost the same significance.

The normal platelet count was found between the limits of about 150,000 and 250,000 by Fusari, Muir, Determann and Helber; between the limits of about 200,000 and 325,000 by Hayem, Afanassieu, Van Emden and Wright and Kinnicutt; between 266,000 and 469,000 by Pratt; at an average of 500,000 by Pruss; at an average of 635,300 by Brodie and Russell, and between 730,000 and 961,500 by Kemp and Calhoun. It is evident that the last four or five observers included bodies in their counts which the former did not think were platelets. A critical review of methods for counting platelets has been made by Pratt[1] and Wright and Kinnicutt,[2] etc. The results of a series of counts made

*Note.—Results reported in brief before the Johns Hopkins Medical Society, Feb. 19, 1912.

*From the Medical Clinic of Professor v. Romberg, Tübingen, Würtemberg. The author desires to express his thanks to Professor Von Romberg in whose wards and laboratories this work was completed.

1. Pratt, J. H.: A Critical Study of the Various Methods Employed for Enumerating Blood-Platelets. Jour. Am. Med. Assn., Dec. 30, 1905.

2. Wright, J. H. and Kinnicutt, Roger: A New Method of Counting Blood-Platelets for Clinical Purposes. Jour. Am. Med. Assn., lvi, 1457.

according to Wright and Kinnicutt's method by me on four normal individuals during a period of fourteen days, did not differ materially from those of Wright and Kinnicutt. The lowest count was 196,000, the highest 400,000, the average 262,000. The counts are given in detail in Table 9.

Pathologic variation in the platelet count has been attributed to various factors, particularly to blood regeneration, fever and malnutrition. The most constant findings have been: 1. A reduced count during the febrile period of acute diseases and an increased count during convalescence. This change in the count was first observed by Hayem and was called by him a "hematoblastic crisis." It has been noted particularly in pneumonia, typhoid fever and malaria. 2. An increased count in chronic secondary anemia and in splenomyelogenous leukemia, and a reduced count in pernicious anemia and lymphocytic leukemia. 3. An increased count in chronic diseases, particularly tuberculosis. 4. A reduced count in purpura hemorrhagica. For a review of the literature on the subject the reader is referred to papers by Determann,[3] Helber,[4] Wright and Kinnicutt,[1] W. W. Duke,[5] etc.

My work was undertaken mainly for the purpose of discovering, if possible, some of the factors which give rise to variation in the platelet count. The subject was studied both clinically and experimentally. Interesting changes in the platelet count were observed in diphtheria, tuberculosis and nephritis. L. Selling[6] had previously observed marked changes in the count in benzol poisoning. To throw light on the findings in humans, animals were treated with varying quantities of diphtheria toxin, tuberculin and benzol and the effect of these substances on the platelet count noted.

METHODS

Rabbits were the animals used. It was observed in experiments carried out by me in the Hunterian Laboratory of Experimental Pathology that rabbits were better adapted to the study of blood-platelets than dogs. The changes in the count are more rapid and extreme, the bone-marrow is free from spicules of bone, and is, therefore, easier to mount for

3. Determann: Klinische Untersuchungen über Blutplättchen. Arch. f. klin. Med., 1898, p. 365.

4. Helber, E.: Ueber die Zählung der Blutplättchen im Blute des Menschen und ihr Verhalten bei pathologischen Zuständen. Deutsch. Arch. f. klin. Med., 1904, xxxi, 316.

5. Duke, W. W.: The Pathogenesis of Purpura Hemorrhagica. THE ARCHIVES INT. MED., 1912. Not yet published.

6. Selling, L.: A Preliminary Report of Some Cases of Purpura Hemorrhagica Due to Benzol Poisoning. Bull. Johns Hopkins Hosp., 1910, xxi, No. 227; Benzol als Leukotoxin (Studien über die Degeneration und Regeneration des Blutes und der hematopoetischen Organe). Beitr. z. path. Anat. u. z. allg. Path. 1911, li, 576.

microscopic study, and rabbits show fewer ill effects following the administration of benzol than dogs.

The platelet counts were made by Wright and Kinnicutt's method,[1] with precautions mentioned by me[7] in a previous paper. Platelets in rabbits vary greatly in size, especially under the influence of diphtheria toxin and benzol. Sometimes the majority are as large as human platelets, sometimes almost as small as bacteria. Great care in the technic had to be used before constant results were obtained. Points to which especial attention was paid were scrupulous cleanliness; careful balancing of the proportions of cresyl blue and potassium cyanid used in the diluting fluid so as to give the platelets a lead blue color and avoid the precipitation of stain; and the collection of blood for the counts from hemorrhage which flowed freely from fresh cuts in the ear veins.

To those who wish to familiarize themselves with the appearance of platelets the following procedure is suggested: Allow blood to flow freely across a clean glass slide for about three minutes. Wash away the excess of blood with Wright and Kinnicutt's diluting fluid or a decalcifying solution. Cover with a cover-glass. Examine with a high dry or oil immersion lens. Such a preparation contains myriads of platelets.

The platelet count determined by me once in eighteen normal rabbits fell between 380,000 and 1,200,000. The average was 757,000. Some normal rabbits have high counts, others have low ones. Change in environment is occasionally followed by a change in the count, which may amount to as much as 50 per cent. of the original count. For this reason the animals used in my experiments were kept under constant conditions for a few days before observations were started. Fluctuations were then not great enough to interfere with the value of the experimental results.

THE EFFECT OF DIPHTHERIA TOXIN[8] ON THE PLATELET COUNT

SERIES 1.—In Table 1 are recorded results showing the effect on the platelet count of doses of diphtheria toxin which caused death in rabbits in three to four days. In this series of experiments, two doses of diphtheria toxin (0.04 gm. in 2 c.c. of sterile salt solution) were given subcutaneously to three medium-sized rabbits on two successive days. On the day following the second dose the animals were very quiet and sick. The ears were cold and the ear vessels so constricted that blood for the platelet count was obtained with difficulty. On the third or fourth days after the first injection the animals died.

Autopsies: The renal epithelium was degenerated in high degree. The bone-marrow was red and soft. The marrow cells had a pathologic appearance. The nuclei of a majority of the megakaryocytes were vacuolated or pyknotic.

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7. Duke, W. W.: The Rate of Regeneration of Blood-Platelets. Jour. Exper. Med., 1911, xiv, No. 3, p. 265.

8. The diphtheria toxin used in these experiments was prepared and given to me by the Hoechst Farbwerk. For this I desire to express my thanks.

TABLE 1.—THE EFFECT OF LARGE DOSES OF DIPHTHERIA TOXIN ON THE PLATELET COUNT

Experiment No.		24	25	26	
Weight of Rabbit...		2.5 Kg.	2.5 Kg.	2.5 Kg.	
Date	Dose of Toxin, Gm.	Platelet Counts			Remarks
July—					
28	....	920,000	810,000	1,200,000	.....
29	0.04	970,000	700,000	860,000	.....
30	0.04	660,000	960,000	1,250,000	Animals lively.
31	....	200,000	335,000	275,000	Animals sick.
Aug.—					
1	....	Found dead.	Found dead.	390,000	Exp. 26. Leuko., 20,000.
2	....			Found dead.	.....

SERIES II.—In Table 2 are recorded results showing the effect on the platelet count of fatal doses of diphtheria toxin but smaller doses than those used in the previous series. One dose of diphtheria toxin (0.02 gm. in 1 c.c. of sterile salt solution) was given subcutaneously to three very large rabbits. The animals were rather quiet after the third day following the inoculation but did not appear very ill. In each case death occurred rather unexpectedly.

The bone-marrow changes found in these animals at autopsy were not so marked as in the animals of the previous series. The marrow was firm and pink. The cells were less pathologic in appearance.

TABLE 2.—THE EFFECT OF FATAL BUT SMALLER DOSES OF DIPHTHERIA TOXIN ON THE PLATELET COUNT

Experiment No.		27	28	29	
Weight of Rabbit...		4 Kg.	4 Kg.	3 Kg.	
Date	Dose of Toxin, Gm.	Platelet Counts			Remarks
June—					
2	....	.....	.....	640,000	.....
3	0.02	400,000	830,000	600,000	.....
4	....	310,000	660,000	690,000	Animals lively.
5	....	.....	.....	.....	Animals quiet.
6	....	640,000	Found dead.	440,000	Animals quiet.
7	....	640,000	.....	480,000	Animals quiet.
8	....	1,400,000	.....	Found dead.	Animals quiet.
9	....	1,040,000	.....	.....	.....
10	....	Found dead.	.....	.....	.....

SERIES III.—In Table 3 are recorded results showing the effect of sublethal doses of diphtheria toxin on the platelet count. Three small doses of diphtheria toxin (0.0012 gm. to 0.0024 gm. in 1 to 2 c.c. of sterile salt solution) were given subcutaneously to three moderate-sized rabbits. The administration was discontinued as soon as the animals began to show symptoms of poisoning. These symptoms were very slight and lasted but a few days. The animals seemed more quiet than usual and the ears were cold. After two or three days the animals were again lively and strong and remained so throughout the experiment. Each animal was anemic toward the end of the experiment. On June 19 the hemoglobin (Sahli) and white count were respectively 55 per cent. and 8,000 in Animal 33, 25 per cent. and 16,000 in Animal 34, and 50 per cent. and 5,000 in Animal 35. The majority of the leukocytes in each case were polymorphonuclear neutrophils. No blasts were seen. Animal 34 June 26 to 30 had severe purpura hemorrhagica. This experiment has been described and discussed fully in a previous paper.[2] Hemorrhagic diathesis in this case seems to have been the result, not the cause, of the reduced number of platelets. No paralysis was observed. The animals were apparently in good condition at the end of the experiment.

TABLE 3.—THE EFFECT OF SUBLETHAL DOSES OF DIPHTHERIA TOXIN ON THE PLATELET COUNT

Experiment No.		33	34	35
Weight of Rabbit		2.5 Kg.	2.5 Kg.	2 Kg.
Date	Dose of Toxin, Gm.	Platelet Counts		
June—				
13	.....	580,000	430,000	1,100,000
14	0.0012	540,000	620,000	400,000
15	.....	500,000	600,000	920,000
16	0.0018	540,000	570,000	1,090,000
17	0.0024	630,000	560,000	1,080,000
18	.....	860,000	690,000	1,370,000
19	.....	1,150,000	690,000	1,300,000
20	.....	1,200,000	930,000	1,900,000
21	.....	1,280,000	860,000	1,700,000
22	.....	1,270,000	970,000	1,600,000
23	.....	1,420,000	1,700,000	1,900,000
24	.....	1,210,000	1,040,000	2,040,000
25	.....	920,000	440,000	1,400,000
26	.....	1,080,000	4,000	1,300,000
27	.....	1,190,000	4,000	1,140,000
28	.....	1,000,000	8,000	1,080,000
29	.....	650,000	64,000	480,000
30	.....	720,000	100,000	890,000
July—				
1	.....	930,000	150,000	1,360,000
2	.....	940,000	250,000	1,560,000
3	.....	920,000	380,000	1,540,000
4	.....	860,000	460,000	1,640,000
5	.....	1,110,000	370,000	1,680,000
6	.....	.....	.....	.....
7	.....	1,160,000	550,000	2,080,000
8	.....	.....	.....	.....
9	.....	.....	200,000	.....
10	.....	.....	.....	.....
11	.....	860,000	330,000	1,320,000
12	.....	.....	.....	.....
13	.....	.....	230,000	.....

SUMMARY OF EXPERIMENTS WITH DIPHTHERIA TOXIN

The inoculation of rabbits with diphtheria toxin in doses which proved fatal in from three to four days, was followed by a rapid fall in the platelet count to about one-third of the normal. Degeneration of the bone-marrow was found at autopsy. The nuclei of the megakaryocytes were vacuolated and picnotic. The results are shown graphically in Chart 1.

The inoculation of fatal but smaller doses of toxin gave results which were not so marked nor constant as those following the use of the larger and smaller doses. The bone-marrow changes were not so marked as those of the previous series. The results are shown graphically in Chart 2.

The inoculation of rabbits with sublethal doses of toxin was followed by, first, a rise in the count which reached, in one case, a height of 2,000,000; then a rapid fall in the count which reached in one instance the low level of 4,000; and finally, by a return of the count to normal, or by a rise above normal, which persisted for a number of days. Severe sec-

ondary anemia developed in each animal toward the end of the experiment. One animal had severe purpura hemorrhagica during the period in which the platelet count was at its lowest. This result is thought to be the effect, not the cause, of the diminished number of platelets. It has been discussed fully in a previous paper.[8] The results are shown graphically in Chart 3.

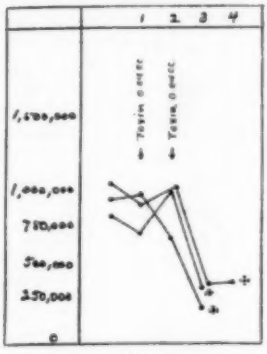

Chart 1

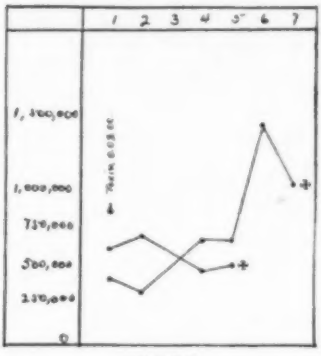

Chart 2

Chart 1.—The effect of large doses of diphtheria toxin on the platelet count in three rabbits.

Chart 2.—The effect of smaller but fatal doses of diphtheria toxin on the platelet count in two rabbits.

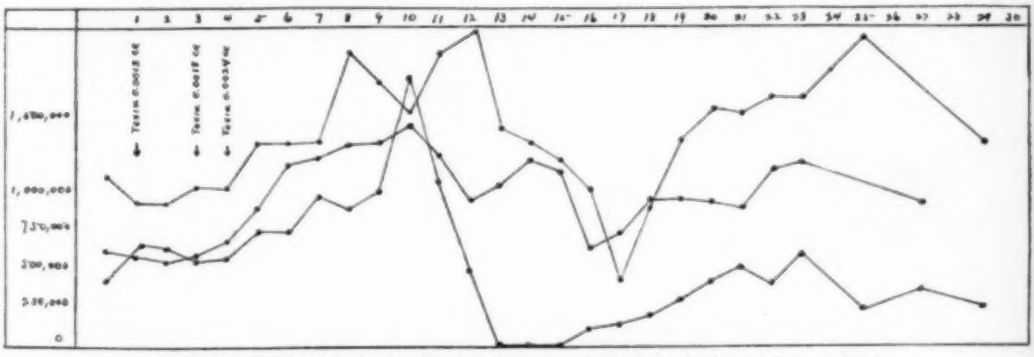

Chart 3.—The effect of sublethal doses of diphtheria toxin on the platelet count in three rabbits.

THE EFFECT OF BENZOL ON THE PLATELET COUNT[9]

SERIES I.—In Table 4 are recorded results showing the effect on the platelet count of doses of benzol which proved fatal in about eleven days. In this series of experiments Merck's benzol was injected intramuscularly in two rather small

9. The author wishes to thank Dr. L. Selling for his kind suggestions regarding the use of benzol.

rabbits for a period of five days in daily doses of 2 c.c. The animals at first showed no noticeable ill effects following this procedure. After about the fourth day, however, it was observed that the ears were cold, that the animals were quiet and seemed weak and sick. There was noted also loss of hair, loss of weight and anemia. The hemoglobin was 60 per cent., Sahli, in Rabbit 23 on May 23. No abscesses developed in these rabbits. In dogs treated with benzol in experiments carried out by me in the Hunterian Laboratory of Experimental Pathology there was observed in addition to the symptoms just mentioned, weak, wobbling gait, tremor, paralysis, jaundice, a mild tendency to bleed, and lipemia. On the twelfth day after the first inoculation with benzol Animal 23 was found dead and Animal 22 was killed.

At autopsy was found anemia and fatty degeneration of the organs and almost complete aplasia of the bone marrow. Megakaryocytes were hardly to be found.

TABLE 4.—THE EFFECT OF FIVE 2 C.C. DOSES OF BENZOL ON THE PLATELET COUNT IN TWO RABBITS

Experiment No.		22		23	
Approx. Weight of Rabbit		1 Kg.		1 Kg.	
Date	Dose of Benzol, c.c.	Platelet Count	White Count	Platelet Count	White Count
May—					
13	2	340,000	....	425,000	6,600
14	2	.....	....	416,000	9,800
15	2	.....	....	608,000	9,200
16	2	.....	....	740,000	11,000
17	2	500,000	6,000	1,230,000	3,300
18	..	.....	....	990,000	550
19	..	.....	....	1,000,000	880
20	..	860,000	1,600	280,000	2,700
21	..	300,000	3,400	72,000	1,200
22	..	120,000	5,000	56,000	1,600
23	..	61,000	....	63,000	1,000
24	..	Animad killed	....	Found dead.	....

TABLE 5.—THE EFFECT OF THREE 2 C.C. DOSES OF BENZOL ON THE PLATELET COUNT IN TWO RABBITS

Experiment No.		36	38
Weight of Rabbit		1.5 Kg.	1.5 Kg.
Date	Dose of Benzol, c.c.	Platelet Counts	
July—			
24	.....	520,000	800,000
25	.....	520,000	780,000
26	.....	730,000	880,000
27	2.00	690,000	900,000
28	2.00	.....	780,000
29	.....	.....	.....
30	2.00	820,000	680,000
31	.....	.....	.....
Aug.—			
1	.....	910,000	810,000
2	.....	.....	.....
3	.....	.....	.....
4	.....	720,000	650,000
5	.....	.....	.....
6	.....	.....	.....
7	.....	1,220,000	1,000,000
8	.....	.....	.....
9	.....	1,780,000	710,000
10	.....	.....	.....
11	.....	1,330,000	1,380,000
12	.....	.....	.....
13	.....	1,320,000	1,060,000

SERIES II.—In Table 5 are recorded results showing the effect of fewer doses of benzol on the platelet count. In this series of experiments three 2 c.c. doses of benzol were given intramuscularly to two moderate-sized rabbits. Animals 30 and 32 of the tuberculin experiments were used. The symptoms observed were the same as those of the previous series but less severe. Subcutaneous abscesses formed in each case. The animals were in fairly good condition at the end of the experiment.

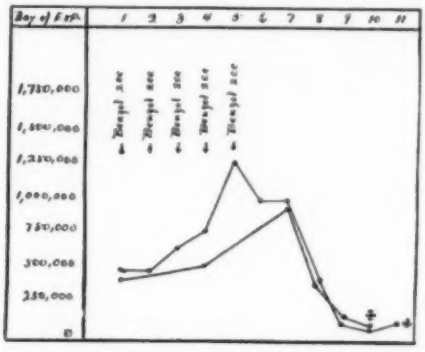

Chart 4.—The effect of five 2 c.c. doses of benzol on the platelet count in two rabbits.

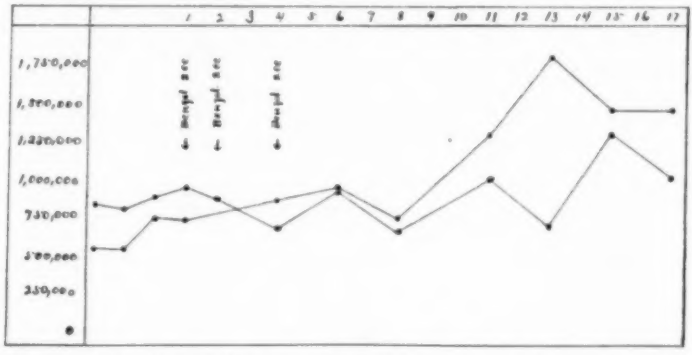

Chart 5.—The effect of three 2 c.c. doses of benzol on the platelet count in two rabbits.

SUMMARY OF EXPERIMENTS WITH BENZOL

The inoculation of rabbits with benzol in doses which proved fatal in about eleven days was followed by, first, a rise in the platelet count (in one case to a height of 1,230,000), then a rapid fall in the count (in one case to a level of 61,000). Severe anemia developed in each animal toward the end of the experiment.

The bone-marrow at autopsy was almost completely aplastic. Megakaryocytes could hardly be found. The results are shown graphically in Chart 4.

The inoculation of rabbits with benzol in doses which did not prove fatal within twenty days was followed by a gradual rise in the platelet count (in one case to a height of 1,780,000). The count did not fall below normal in either animal during the time of the experiment (seventeen days). The results are shown graphically in Chart 5.

THE EFFECT OF TUBERCULIN ON THE PLATELET COUNT

SERIES I.—In Table 6 are recorded results showing the effect of tuberculin on the platelet count. The doses given in this series were large but were the smallest used in this work. Five doses of Koch's old tuberculin (0.1 to 0.2 gm. in 1 to 2 c.c. of a solution of dilute phenol) was given intramuscularly to three medium-sized rabbits. After a lapse of thirty-two days 0.5 gm. was given. The animals suffered no apparent ill effect from the tuberculin. They remained strong and lively throughout the experiment.

TABLE 6.—THE EFFECT OF THE SMALLER DOSES OF TUBERCULIN ON THE PLATELET COUNT IN RABBITS

Experiment No.		21	22	23
Weight of Rabbit		2.5 Kg.	2 Kg.	2 Kg.
Date	Dose of Tuberculin, Gm.	Platelet Counts		
May—	.....	1,080,000	520,000	....
29	..	1,200,000	480,000	740,000
30	0.1	900,000	400,000	660,000
31	0.1	1,730,000	590,000	720,000
June—				
1	0.1	1,300,000	610,000	960,000
2	0.15	1,500,000	730,000	940,000
3	0.2	1,370,000	720,000	800,000
4	..	1,000,000	530,000	710,000
5	..	.....	....	.....
6	..	920,000	600,000	600,000
7	..	.....	.....	.....
8	..	.....	.....	.....
9	..	1,140,000	.....	720,000
10	..	.....	.....	.....
11	..	.....	.....	.....
12	..	.....	.....	.....
13	..	.....	840,000	570,000
July—		.....		
5	0.5	.....	1,100,000	650,000
6	..	.....	640,000	700,000
7	..	.. ..	810,000	800,000
8	..	.....	.....	.....
9	..	.....	740,000	760,000
10	..	.....	.....	.....
11	..		880,000	660,000

SERIES II.—In Table 7 are recorded results showing the effect of larger doses of tuberculin on the platelet count. Tuberculin gm. 1.0 undiluted was given intramuscularly to three rather small rabbits. On the fifth day after the inoculation the animals seemed a little sick and quiet. After two or three days they seemed lively and strong again and remained so throughout the experiment.

TABLE 7.—THE EFFECT OF LARGER DOSES OF TUBERCULIN ON THE PLATELET COUNT IN RABBITS

Experiment No.		30	31	32
Weight of Rabbit		1.5 Kg.	1.5 Kg.	1.5 Kg.
Date	Dose of Tuberculin, Gm.		Platelet Counts	
June—			440,000	340,000
14	1.0	590,000	420,000	380,000
15	..	650,000	410,000	390,000
16	..	520,000	405,000	420,000
17	..	720,000	620,000	1,080,000
18	..	900,000	580,000	830,000
19	..	.....	.....	.....
20	..	1,200,000	840,000	960,000
21	..	600,000	770,000	800,000
22	..	550,000	570,000	800,000
23	..	630,000	500,000	800,000
24	..	520,000	470,000	860,000
25	..	520,000	510,000	780,000
26	..	730,000	580,000	880,000
27	..	690,000	430,000	900,000

SERIES III.—In Table 8 are recorded results showing the effect of the largest doses of tuberculin on the platelet count. Gm. 3.0 of tuberculin undiluted was given intramuscularly to three small, young rabbits. The dose in this series was gm. 3.0 per kilo of weight. For one or two days after the inoculation the animals seemed quiet and sick but on the third day were again lively. After a period of one week, there was noticeable loss of weight and at the end of the experiment emaciation was quite marked. Ulceration developed on the hind legs of each animal at the end of the first week and finally the legs seemed almost to dry up. The ears also withered toward the end of the experiment and blood could be obtained only by cutting the largest vessels. Severe anemia developed in each animal toward the end of the experiment.

TABLE 8.—THE EFFECT OF LARGE DOSES OF TUBERCULIN (3 GM. PER KILO OF WEIGHT) ON THE PLATELET COUNT IN RABBITS

Experiment No.		36	37	38
Weight of Rabbit		1 Kg.	1 Kg.	1 Kg.
Date	Dose of Tuberculin, Gm.		Platelet Counts	
July—				
22	..	980,000	960,000	1,200,000
23	3.0	830,000	790,000	1,320,000
24	..	860,000	650,000	880,000
25	..	730,000	800,000	1,030,000
26	..	1,290,000	780,000	1,113,000
27	..	1,100,000	1,070,000	1,360,000
28	..	.....	.....	.....
29	..	910,000	810,000	.....
30	..	.....	.....	.....
31	..	.....	.....	.....
Aug.—				
1	..	900,000	600,000	1,900,000
2	..	.....	.....	.....
3	..	1,880,000	530,000	1,920,000
4	..	2,200,000	820,000	2,320,000
5	..	1,720,000	830,000	1,600,000
6	..	Found dead	.....	.....
7	..	.....	740,000	Found dead

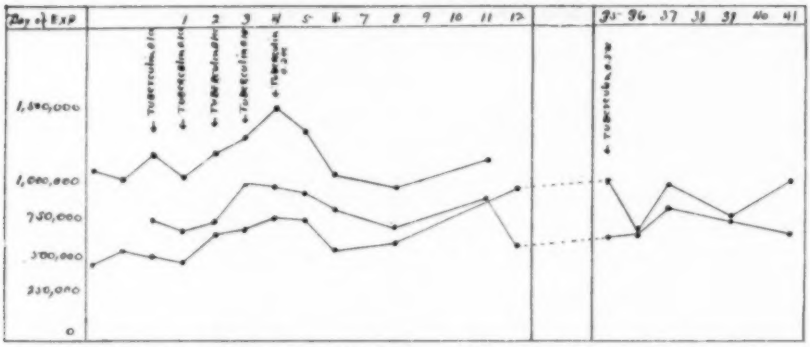

Chart 6.—The effect of tuberculin in doses of about gm. 0.25 per kilo of weight on the platelet count of three rabbits. Gm. 0.6 was given in divided doses during a period of five days. After an interval of thirty-two days a second dose of gm. 0.5 was used.

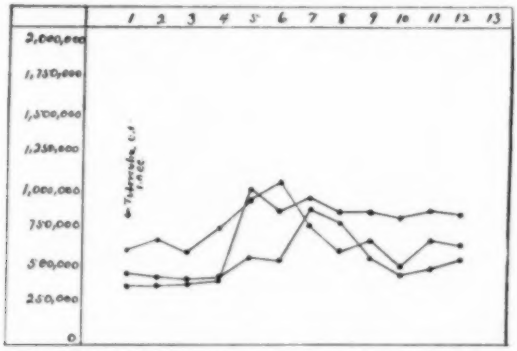

Chart 7.—The effect of tuberculin gm. 0.7 per kilo of weight on the platelet count of three rabbits.

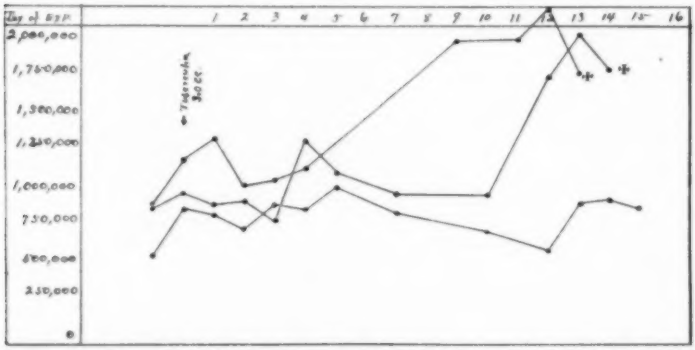

Chart 8.—The effect of tuberculin gm. 3.0 per kilo of weight on the platelet count of three rabbits.

SUMMARY OF EXPERIMENTS WITH TUBERCULIN

The inoculation of animals with large doses of tuberculin was followed by a rise in the platelet count in nearly every instance. The change in the counts was in general not so marked as that observed in the previous experiments. The most striking result followed the use of the largest doses (3 gm. per kilo of weight), in two of which experiments the count reached a height of more than 2,000,000. The count did not fall below normal in a single instance. Severe anemia developed in the animals receiving the largest doses. The results are shown graphically in Charts 6, 7 and 8.

DISCUSSION OF RESULTS

In a previous paper it was suggested by me that platelets were probably very short-lived bodies, or what amounts to the same thing, that platelets either disintegrate or are utilized and regenerated in enormous numbers daily. This view, while not directly proved, harmonizes well with facts as known at present. The facts are as follows:

1. The platelet count under normal conditions is relatively more variable than the red count. A comparison between the two is well shown in Table 9, in which are recorded a series of platelet counts made by me in four normal individuals, and in Table 10, in which are recorded series of red counts made by Professor Bürker.[10]

TABLE 9.—PLATELET COUNTS IN FOUR NORMAL INDIVIDUALS

Date	1	2	3	4
May—				
9	275,000	295,000	290,000	315,000
10	.....	.....	.....	.....
11	.....	.....	.....	.....
12	220,000	300,000	280,000	240,000
13	.....	.....	.....	.....
14	.....	280,000	.....	.....
15	.....	270,000	.....	190,000
16	225,000	300,000	300,000	.....
17	.....	.....	.....	220,000
18	.....	240,000	.....	190,000
19	230,000	.....	350,000	.....
20	225,000	.....	275,000	.....
21	.....	260,000	.....	.....
22	196,000	.....	400,000	.....
23	220,000	.....	.....	.....
24	240,000	.....	250,000	.....
Highest count	275,000	300,000	400,000	315,000
Lowest count	196,000	240,000	250,000	190,000
Average	224,000	264,000	306,000	231,000

10. K. Bürker: Ueber weitere Verbesserungen der Methode zur Zählung roter Blutkörperchen nebst einigen Zählresultaten. Pflügers Archiv. f. ges. Physiol., 1911, cxlii, 337.

TABLE 10.—THE RED COUNT IN NORMAL PERSONS AS OBSERVED BY PROFESSOR BÜRKER

Period I*	Period II	Period III
5,250,000	5,470,000	5,420,000
5,370,000	5,270,000	5,320,000
5,320,000	5,280,000	5,150,000
5,330,000	5,370,000	5,360,000
5,200,000	5,430,000	5,220,000
5,170,000	5,400,000	5,410,000
5,120,000	5,250,000	5,430,000

Highest count 5,470,000. Lowest count 5,120,000. Average 5,320,000.

*The counts were made on successive days in the same individual at three periods about five weeks apart.

2. The platelet count when pathologically increased or decreased is more variable than the count under normal conditions. Daily fluctuations may be as great as the normal count. Results recorded in Table 11, obtained from patients with advanced phthisis (A) and severe nephritis (B), both observed by me in the clinic of Professor Romberg, are given as examples. The red count is never subject to such great and rapid changes as these.

TABLE 11.—PLATELET COUNTS IN A PATIENT WITH (A) ADVANCED PHTHISIS, (B) SEVERE NEPHRITIS

A		B	
Date	Platelet Counts	Date	Platelet Counts
June—		May—	
14	210,000	9	1,260,000
18	4,000	10	1,120,000
20	10,000	12	760,000
21	1,000*	16	575,000
22	110,000	19	535,000
23	210,000	24	510,000
24	295,000	25	540,000
25	330,000	26	640,000
26	385,000	28	760,000
27	520,000	29	800,000
28	550,000	June—	
30	720,000	1	786,000
July—		8	560,000
1	720,000	15	400,000
7	640,000	16	350,000
12	400,000	25	1,400,000
17	500,000	July—	
		3	900,000
		5	500,000

3. It was demonstrated by me[7] in the Hunterian Laboratory of Experimental Pathology and in the pathological laboratory of the University of Kansas that the total number of platelets in the blood of dogs can be regenerated within a period of from three to five days. To prove this dogs were bled in amounts of 200 to 250 c.c. The blood was defibrinated and reinjected intravenously. This process was repeated frequently at short intervals, so that finally the fibrinogen of the circulating blood was

reduced to a trace. Platelets are removed from the blood by defibrination. The platelet count of these animals was therefore also reduced to a minimum. Counts were made at short intervals after the operation, and the rate at which it returned to normal was observed. In each of the five experiments the count reached normal within from three to five days. The results obtained in two of these experiments are shown graphically in Chart 9. As compared with the rate of regeneration of red cells in a condition somewhat analogous (secondary anemia), that of the platelets is much more rapid. The regeneration of the total number of platelets in the blood is a matter of days, while the regeneration of about 50 per cent. of the red cells is a matter of weeks. The relatively slow rate at which red cells are regenerated in dogs when their number is reduced by bleeding and injection of salt solution, is shown in Chart 10, in which are recorded graphically the results obtained by Dr. P. M. Dawson.[11]

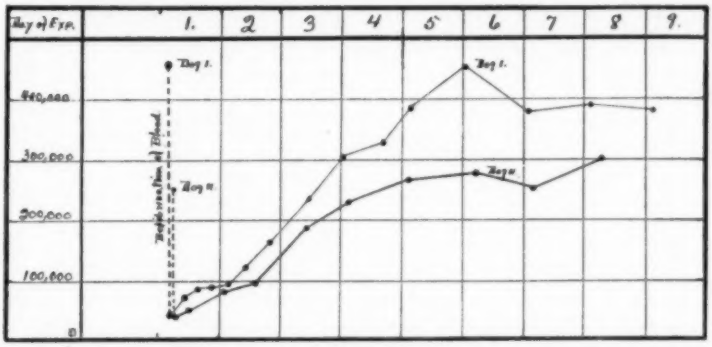

Chart 9.—About 90 per cent. of the platelets in two dogs were removed from the circulation by withdrawing, defibrinating and reinjecting 200 c.c. amounts of blood six to ten times during a period of four hours. The chart shows the rapid rate at which the count rose after it was thus reduced. It reached normal in one animal on the fourth day; in the other on the fifth.

4. In a previous paper[12] I reported results obtained from the study of two patients observed in the Massachusetts General Hospital, who had hemorrhagic disease. Both patients had very low platelet counts (3,000 to 20,000). Following direct transfusion of blood, the counts were found to be 123,000 and 89,000, respectively. The increase in the count was due evidently to the introduction of the donor's platelets into the patient's circulation. The counts fell again rapidly after transfusion and within three days reached their previous low level. The red counts, also increased by the transfusion, remained high for a period of weeks.

11. Dawson, P. M.: Effects of Venous Hemorrhage and Intravenous Infusion in Dogs. Am. Jour. Physiol., 1900, iv, No. 1.

12. Duke, W. W.: The Relation of Blood-Platelets to Hemorrhagic Disease. Jour. Am. Med. Assn., 1910, lv, 1185.

The following experiment was performed by me in the Hunterian Laboratory of Experimental Pathology: A dog was treated for six days with intramuscular injections of benzol. The platelet count at the beginning of the experiment was 284,000. Three days after the last dose of benzol the count was 26,500. The animal was then bled and transfused by the Crile method.[13] An animal of the same breed was used as donor. Immediately after transfusion the platelet count was 179,000. Twenty-four hours later it had fallen to 110,000. The red count was also increased by transfusion and remained high. This experiment was, of course, incomplete. It is reported simply in confirmation of the results obtained in humans.

The above facts admit several possible interpretations. At present the following seems to me the most logical. Future work may prove it erroneous.

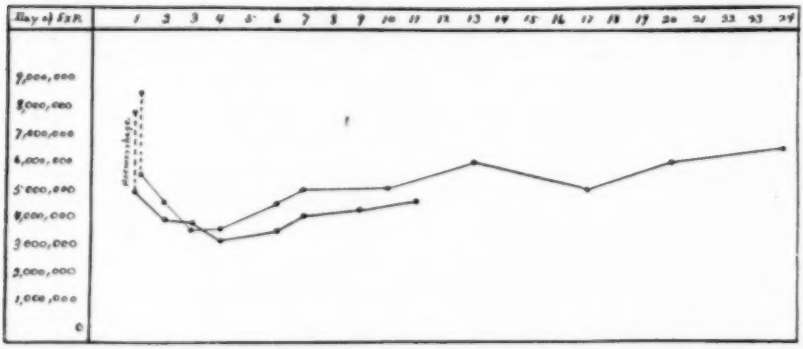

Chart 10.—Results of Dr. P. M. Dawson. The red count in two dogs was reduced by withdrawing a large amount of blood and replacing it with salt solution. The chart shows the relatively slow rate at which the red counts rose after they were thus reduced. They did not reach normal in three weeks. The conditions of these experiments and of those of Chart 9 would seem to be somewhat analogous.

Let us assume that the average length of life of platelets in a given individual is four days. If the platelet count were 400,000, we could suppose that in this individual about 100,000 platelets disintegrated and were regenerated daily. If now the rate of formation of platelets were suddenly doubled through the action of some stimulating agent, the count would rise rapidly to 800,000, and if made fivefold would rise in a few days to 2,000,000; that is, if the platelets formed under the new conditions lived out the same life cycle as those formed under normal conditions. If now the increase in the count to 2,000,000 were brought about by an agent which first stimulated, then paralyzed the production

13. The transfusion was carried out by Dr. W. D. Gatch, to whom I desire to express my thanks.

of platelets, a fall in the count at an average rate of 500,000 a day would take place the day the paralysis was complete. If the paralysis occurred suddenly the count would fall from 2,000,000 to 0 within a period of four days. The fundamental point in this assumption is that the life cycle of the platelet is short; that is, that platelets are destroyed and regenerated in enormous numbers daily. Let us see how it conforms to actual fact.

It would harmonize with the fact that the platelet count is less constant than the red count. If the daily disintegration of platelets is 25 per cent. of the total number in the blood, one would expect that the count would be less constant than the red count where the daily disintegration is relatively much less in amount. Likewise, it would harmonize with the fact that platelets can increase or decrease in number so rapidly in various pathologic and experimental conditions. A pathologic rise or fall in the count at the rates observed (often 500,000 per day) would not seem remarkably great if the normal rate of formation were 100,000 per day. If, however, the normal rate of formation were say 20,000 per day, a pathologic rise or fall such as that mentioned would seem very large (twenty-five times the normal rate). If the latter were true, we would have to assume that fluctuations observed in my experiments were the effects of agents highly stimulating or destructive. This is of course a possibility, but does not harmonize well with all our facts. The same reasoning may be applied in accounting for the fact that the platelets introduced into the circulation of the patients with hemorrhagic disease to which I referred, disappeared so rapidly. In this case we had normal platelets in plasma, which may or may not have been destructive to them. If the life cycle of the platelet is normally short, the rapid disappearance was a more or less physiologic incident; if the life cycle is normally long, the platelets must have been destroyed prematurely.

While the assumption of either a short or long life cycle for platelets may be consistent with the results already mentioned, that of a normally long life would not account well for the fact that platelets can be regenerated so rapidly after their removal from the circulation by repeated defibrination of the blood. Such a view would suppose that the experimental condition led to a rate of generation of platelets which was much greater than the normal. This is, however, possible. It may be that a lack of platelets or some other condition in the experiments was a powerful stimulus to platelet generation. It may be repeated, however, that analogous stimulation to the formation of erythrocytes (the lack of red cells in secondary anemia) causes no such rapid rise in the red count.

While I believe that platelets are generated and destroyed at a rapid rate under normal conditions, and that this is a factor which must be constantly borne in mind when one interprets the meaning of pathologic variation in the platelet count, I do not deny that other factors may play a part. For example, in the experiments with large doses of benzol and

diphtheria toxin, it was noted that the platelets became smaller and smaller as the count rose. It is not impossible that platelets in the blood-stream were broken up into smaller pieces by the action of these agents and that this contributed to the rapid rise in the count. It is also possible that these small platelets observed in the experimental conditions disintegrated more rapidly than normal platelets, and that this contributed to the rapid fall in the counts which followed. It is possible that platelets in the circulating blood are destroyed by benzol and diphtheria toxin, and that this gave rise in part to the fall in the counts noted in some of the experiments. It is hard to believe, however, that such occurred in the experiments with diphtheria toxin of Series III. The count did not begin to fall in these animals until ten days or more after the administration of the last dose of toxin, and at that time the animals had apparently recovered from the direct ill effects of the poison. One other possibility must also be mentioned. It is well known that after animals have been treated with a foreign serum or peptone, platelets have a tendency to clump and form capillary plugs. The result is that the platelet count may be considerably reduced. It is possible that a clumping of the platelets occurred in some of my animals and diminished the number in the circulating blood. To me it does not seem probable, however. First, the platelets were always evenly distributed when the blood was mixed with Wright and Kinnicut's solution. Second, the fact that the animals developed anemia and had pathologic changes in the bone-marrow suggests another cause for the fall in the counts. Further experiment is necessary, however, before this point can be definitely settled.

The experiments, I believe, can best be interpreted as follows:

Diphtheria toxin in large doses is immediately poisonous to the bone marrow —possibly also to the platelets in the blood stream—and causes an immediate fall in the platelet count.

Benzol, as administered in the experiments of Series I (that is in large doses), and diphtheria toxin as administered in the experiments of Series III (that is, in sublethal doses), act first as stimulants and then as poisons to the progenitors of platelets, thus causing first a rise and then a fall in the platelet count. It may be that platelets themselves are also affected by these agents and that this factor contributes to the change in the counts. It is believed that the rapidity of the changes can be accounted for best by assuming that platelets normally are short-lived bodies.

Benzol, as administered in the experiments of Series II (that is, in smaller doses), and tuberculin act for a period of ten days or more, as stimulants to the formation of platelets. No evidence of a poisonous effect during this period was observed in my experiments. In two of the experiments with diphtheria toxin of Series III, the irritating effect of the poison was greater and more lasting than the poisonous effect. The actual result was an increase in the platelet counts. It seems likely that still smaller doses would produce an irritant effect only.

The experimental work gives us a clearer conception of some of the processes which cause variation of the platelet count and enables us to understand better the findings in humans. In the Children's Hospital of Professor Escherich I made a number of platelet counts on patients with diphtheria. As a rule, the count was reduced during the febrile period of the disease (lowest count 3,000) and increased during convalescence (highest count 750,000). The opposite change, however, was also observed; that is, an increase in the count during the febrile period and a reduction in the count after the clearing of the membrane. The counts then followed the phases of Hayem's crisis as a rule, but the reverse of this also occurred. Examination of Chart 11, in which is recorded graphically the effect of varying doses of diphtheria toxin on the platelet count, shows strikingly that under the influence of diphtheria toxin the platelet count may range at almost any level at almost any time. The behavior

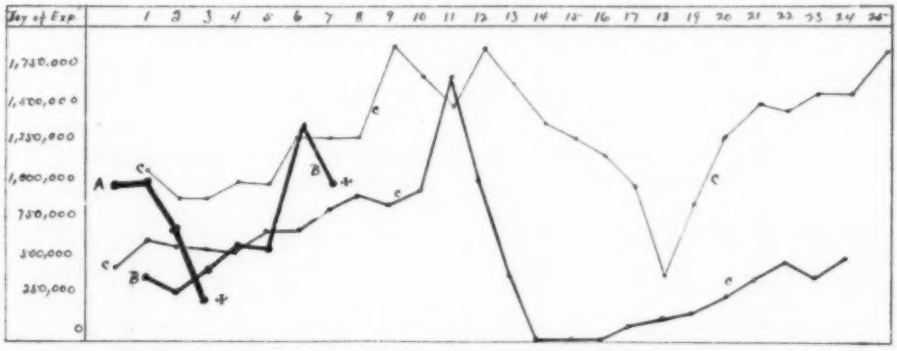

Chart 11.—The effect of diphtheria toxin in varying dosage on the platelet count in rabbits. (A) Largest dose. (B) Smaller but fatal doses. (C) Sublethal doses.

of the count depends on the amount of the toxin administered, and possibly also to a slight extent on the individual resistance of the animal. It suggests that Hayem's crisis in humans with diphtheria is the result of a large amount of toxin, and that the reverse change is the effect of a smaller amount. Low counts would indicate a greater toxemia than high counts, and low counts early in the disease a more severe case than low counts late in the disease.

I made a number of platelet counts on patients with phthisis and nephritis in the medical clinic of Professor Romberg. The platelet count in patients with advanced phthisis was as a rule increased; occasionally very much so (highest count 1,000,000). In two cases it was greatly reduced for a short time (in one case to 55,000; in another to less than 1,000). In patients with severe nephritis and urinary retention the

count was increased as a rule—occasionally very much increased (highest count 1,260,000). In no case was it reduced. Pratt,[14] however, has reported a case of nephritis in which the platelet count descended to 9,000, and Determann[3] an instance in which the count was 90,000. It would appear that the platelet count may be very much increased or very much decreased in phthisis and nephritis. *In diphtheria, the count is increased and decreased by one and the same agent, diphtheria toxin. It*

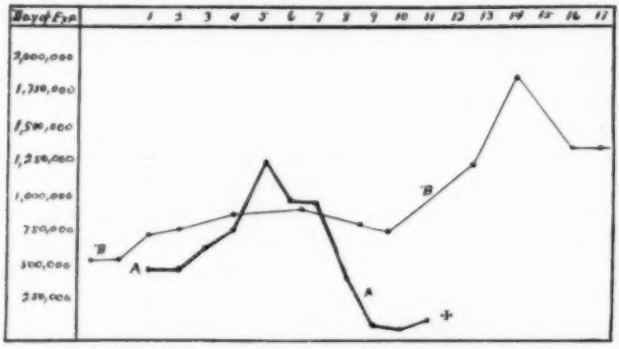

Chart 12.—The effect of benzol in varying dosage on the platelet count in rabbits. (A) Dose fatal in eleven days. (B) Smaller dose.

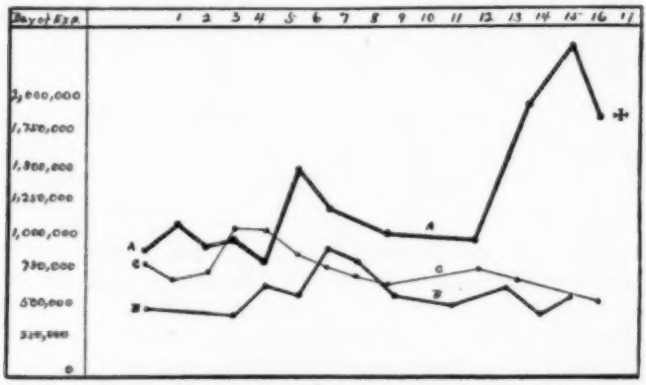

Chart 13.—The effect of tuberculin in varying dosage on the platelet count in rabbits. (A) Largest dose. (B) Smaller dose. (C) Smallest dose.

seems that the high and the low counts of phthisis and possibly also of nephritis and of many other diseases may be likewise the effect of varying quantities of one and the same agent. High counts would seem to be the effect of doses which act as irritants; low counts the effect of poisonous

14. Pratt, J. H.: A System of Medicine. Osler and McCrae, vol. iv, p. 681.

doses. It would appear from the data at hand that where the agent effecting the count is a mild one (such as tuberculin and presumably also the platelet poisons of nephritis or phthisis) the count is increased as a rule, and in rare cases reduced. Where the agent is a stronger one (such as benzol or diphtheria toxin) the counts are more quickly and markedly altered, and low counts (the effect of poisonous doses) are more frequent.

SUMMARY AND CONCLUSIONS

The inoculation of rabbits with doses of diphtheria toxin which proved fatal in three days was followed by an immediate fall in the platelet count to about one-third of the normal. Severe degeneration of the bone-marrow was found at autopsy. The nuclei of a majority of the megakaryocytes were vacuolated or pyknotic.

The inoculation of rabbits with sublethal doses of diphtheria toxin was followed by, first, a rapid rise in the platelet count which reached in one instance a height of 2,040,000, then a rapid fall in the count which reached in one instance the low level of 4,000, and finally by a rise in the count to normal or by a rise above the normal which persisted for a number of days. The animals developed severe anemia toward the end of the experiment.

The inoculation of rabbits with five 2 c.c. doses of benzol was followed by, first, a rapid rise in the platelet count in one instance to a height of 1,230,000, then a rapid fall in the count in one instance to 61,000. The animals developed severe anemia. The bone marrow at autopsy was almost completely aplastic. Megakaryocytes were hardly to be found.

The inoculation of rabbits with three 2 c.c. doses of benzol was followed by a gradual rise in the platelet count, in one instance to a height of 1,780,000. The count did not fall below normal during the period in which observations were made.

The inoculation of rabbits with tuberculin was followed in nearly every instance by a rise in the platelet count. The most striking results followed the use of the largest doses (gm. 3 per kilo of weight). In two instances the count exceeded 2,000,000. In no case did the count fall below normal. Severe anemia developed in the animals receiving the largest doses.

These data it is thought, admit the following interpretation: Diphtheria toxin in large doses is immediately poisonous to the bone marrow—possibly also to platelets themselves—and causes an immediate fall in the platelet count.

Benzol in large doses and diphtheria toxin in sublethal doses, act first as stimulants, and then as poisons to the platelet-forming organs and cause thus first a rise and later a fall in the platelet count. It is possible that the platelets themselves are also affected by these agents, and that this contributes to the change in the counts.

Tuberculin in large doses, benzol in small doses and possibly also diphtheria toxin in very small doses, act for a certain period of time only as stimulants to the progenitors of platelets and cause only a rise in the platelet count.

It is believed that both the high counts and the low platelet counts observed by me in humans with diphtheria are caused by the action of varying amounts of one and the same agent — diphtheria toxin. Low platelet counts in this disease would indicate a more severe toxemia than high counts, and low counts early in the disease a more severe case than low counts late in the disease. This reasoning it is believed may apply to other diseases also, and would seem to account for the occurrence of high platelet counts and low platelet counts in the same pathologic conditions.

It has been suggested by several observers that a poverty of the blood in platelets plays a rôle in the pathogenesis of purpura hemorrhagica. The work reported here supports this view. Purpura hemorrhagica of a certain type was observed in every instance (human and experimental) in which the platelet count descended to a certain low level.

The view expressed by me in a previous paper that platelets were probably very short-lived bodies harmonizes with the results reported here and it is believed accounts for the fact that the platelet count can rise and fall with such rapidity.

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